# Electrophilic Aromatic Sulfonation with SO$_3$: Concerted or Classic S$_E$Ar Mechanism?

Gergana Koleva,[†] Boris Galabov,[*,†] Jing Kong,[‡] Henry F. Schaefer III,[‡] and Paul von R. Schleyer[*,‡]

[†]Department of Chemistry, University of Sofia, Sofia 1164, Bulgaria

[‡]Center for Computational Chemistry and Department of Chemistry, University of Georgia, Athens, Georgia 30602, United States
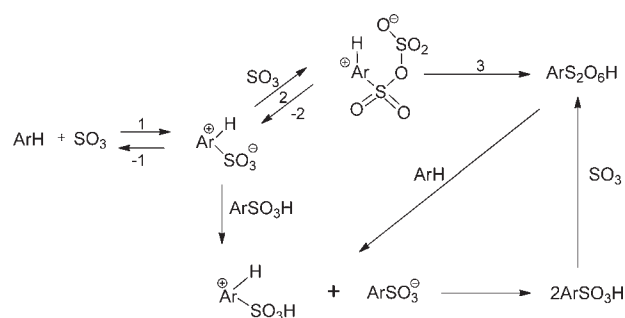
**S** *Supporting Information*

**ABSTRACT:** The electrophilic sulfonation of several arenes with SO$_3$ was examined by electronic structure computations at the M06-2X/6-311+G(2d,2p) and SCS-MP2/6-311+G(2d,2p) levels of theory. In contrast to the usual interpretations, the results provide clear evidence that in nonpolar media and in the absence of catalysts the mechanism of aromatic sulfonation with a single SO$_3$ is *concerted* and *does not involve the conventionally depicted 1:1 σ complex* (Wheland) *intermediate*. Moreover, the computed activation energy for the 1:1 process is unrealistically high; barriers for alternative 2:1 mechanisms involving attack by two SO$_3$ molecules are 12−20 kcal/mol lower! A *direct* 2:1 sulfonation mechanism, involving a *single essential transition state*, but no Wheland type intermediate, is preferred generally at MP2 as well as at M06-2X in isolation (gas phase) or in noncomplexing solvents (such as CCl$_4$ or CFCl$_3$). However, *in polar, higher dielectric SO$_3$-complexing media*, M06-2X favors an S$_E$Ar mechanism for the 2:1 reaction involving a Wheland-type arene-(SO$_3$)$_2$ dimer intermediate. The reaction is slower in complexing solvents, since the association energy, e.g., with nitromethane, must be overcome. But, in accord with the experimental kinetics (second-order in SO$_3$), attack by two sulfur trioxide molecules is still favored energetically over reaction with a single SO$_3$ in CH$_3$NO$_2$. The theoretical results also reproduce the experimental reactivity and regioselectivity trends for benzene, toluene, and naphthalene sulfonation accurately.
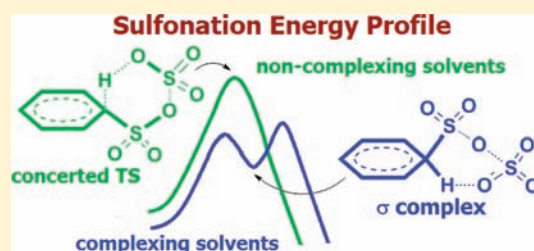
## INTRODUCTION

The electrophilic sulfonation of aromatic compounds is an exceptionally important organic transformation.[1−8] Many reagents, such as sulfuric acid, fuming sulfuric acid, sulfur trioxide, and chlorosulfonic acid, can be utilized.[1−12] Although detailed mechanistic studies have revealed many complexities depending on the reaction conditions (including reversibility and the actual electrophile), SO$_3$, as a free species or complexed to a carrier, is generally considered to be the sulfonating agent (however, see ref 13). It is important to keep in mind that benzene itself is too reactive to study kinetically. But as the sulfonation of 1,3,5-C$_6$H$_3$D$_3$ does not exhibit a primary intramolecular deuterium isotope effect, ipso C−H bond cleavage does not occur in the rate-determining step. Taking advantage of the much lower reactivity of 1,4-dichlorobenzene, Cerfontain[11,12] found that the kinetic order of its sulfonation depends on the solvent: it was first-order in SO$_3$ in noncomplexing CFCl$_3$ solution, but it was second-order in SO$_3$ in CH$_3$NO$_2$. Only second-order kinetics in SO$_3$ were reported for the sulfonation of a few other aromatic substrates in complexing solvents such as CH$_3$NO$_2$, PhNO$_2$, and 1,4-dioxane.[6,11,12] Cerfontain summarized his interpretation of the reaction sequences under various conditions[1−6] by means of Scheme 1.[7] This classic S$_E$Ar mechanism involves a 1:1 Wheland-type arenium zwitterion, ArH$^+$SO$_3$$^−$, as the key intermediate. Either the formation of this σ complex or its further reaction might

**Scheme 1. Reaction Sequence for SO$_3$−Arene Sulfonation Proposed by Cerfontain[7]**

be rate limiting, according to Cerfontain, but the reversible character of S$_E$Ar sulfonation also may be important in determining the kinetics. A 2:1 ArH$^+$(SO$_3$)$_2$$^−$ σ complex also was postulated.

Cerfontain's postulated mechanism in CFCl$_3$ solution, invoking attack by a single SO$_3$ molecule in the rate-determining step to give a zwitterionic σ complex (Wheland-type) intermediate (ArH$^+$SO$_3$$^−$) (Scheme 1),[7] was based on first-order kinetics

**Table 1. Relative Energies and Free Energies (in kcal mol$^{-1}$, at 298.15 K, vs SO$_3$ + benzene) of Critical Structures along the Reaction Paths for the Sulfonation of Benzene with a Single SO$_3$ in the Gas Phase and in Simulated CCl$_4$ and CFCl$_3$ Solutions at M06-2X/6-311+G(2d,2p) and in the Gas Phase and in Simulated CH$_3$NO$_2$ Solution at SCS-MP2/6-311+G(2d,2p)**

| benzene | gas phase M06-2X | | CCl$_4$ solvent[a] M06-2X | | CFCl$_3$ solvent[b] M06-2X | | gas phase MP2 | | CH$_3$NO$_2$ solvent[a] MP2 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $\Delta E$ | $\Delta G$ | $\Delta E$ | $\Delta G$ | $\Delta E$ | $\Delta G$ | $\Delta E$ | $\Delta G$ | $\Delta E$ | $\Delta G$ |
| reactant complex | −7.14 | 0.42 | −6.56 | 0.95 | −7.20 | 0.34 | −6.03 | 1.73 | −4.53 | 5.04 |
| **TS** | 31.08 | 40.87 | 28.14 | 37.81 | 28.15 | 37.88 | 38.90 | 48.51 | 31.79 | 43.86 |
| sulfonic acid | −26.64 | −17.02 | −27.75 | −18.00 | −27.60 | −17.84 | −19.83 | −10.30 | −22.19 | −10.82 |

$^a$ IEF-PCM computations.[28] $^b$ Onsager model computations.[29]

(in SO$_3$) observed only for a single case, 1,4-dichlorobenzene, but not for benzene or any other arene. (As detailed below, we have NOT been able to locate *any* minimum corresponding to this σ complex computationally.) Cerfontain supposed than this ArH$^+$SO$_3^-$ species could survive long enough to react with a second SO$_3$ (step 2) to give another Wheland intermediate of 2:1 composition (ArH$^+$S$_2$O$_6^-$), leading to the final arenepyrosulfonic acid product (ArS$_2$O$_6$H) (step 3). The second-order (in SO$_3$) sulfonation kinetics of 1,4-dichlorobenzene in complexing solvents, nitromethane and 1,4-dioxane,[6,7,12] were consistent with step 2 being rate-controlling. Intramolecular *primary* deuterium isotope effects (i.e., ca. 4 or more) for the sulfonation of a few crowded arenes (such as 1,2,4,5-tetramethylbenzene-3-*D*) in polar solvents suggested that step 3 (which involves C−H(D) bond cleavage) was rate-limiting in such special cases.[7] However, most of the measured intramolecular deuterium isotope effects (including 1,3,5-deuterated benzene) are *secondary* (i.e., close to 1),[5] indicating minimal C−H(D) bond elongation in the TS. Our computed very low activation barrier (see the Supporting Information) rules out the reaction of benzenesulfonic acid with SO$_3$ to give benzenepyrosulfonic acid (shown on the right side of Scheme 1) as a possible rate-controlling stage.

We stress that both the experimental[2,6,7,11] and the prior theoretical (computational) studies of the sulfonation of aromatic compounds[14−18] were based on the classic S$_E$Ar mechanistic interpretation (Scheme 1), where at least the first step involved formation of σ complex (Wheland) intermediates having a tetrahedral ring carbon. In contrast, our work essentially rules out the existence of such 1:1 SO$_3$−arene sulfonation intermediates. Although our computations located alternative, concerted 1:1 SO$_3$−arene reaction mechanisms with 1:1 *transition states* (but not intermediates), all the barriers for such aromatic sulfonation pathways with a single sulfur trioxide molecule in isolation (gas phase) or in noncomplexing solvents are too high to account for the rapid reactions observed experimentally at low temperatures. Thus, 1:1 *transition states* are ruled out as realistic alternatives as well.

Instead, viable mechanisms involve attack by two SO$_3$ molecules; our M06-2X theoretical results reveal two alternative reaction pathways for sulfonation under different conditions. *In isolation* (gas phase) or in nonpolar solvents, such 2:1 reactions follow a concerted pathway involving a single essential transition state (TS) but no Wheland type intermediate. However, *in polar, higher dielectric SO$_3$-complexing media*, the courses of the 2:1 reactions are different; the classic S$_E$Ar mechanism involving Wheland intermediates does dominate the process. Such solvents are expected to have opposing effects; the sulfonation rates should be raised due to the higher dielectric constants but lowered due to the energy needed to disrupt sulfur trioxide−solvent

complexes (cf. Table 4 for representative data for the association of SO$_3$ with one or two CH$_3$NO$_2$'s).[19] Despite the latter effect, the rate is still fast enough to account for the experimental observations.

## ■ COMPUTATIONAL METHODS

The geometries of the reactants, reactant complexes, intermediates, transition states, and products for the SO$_3$ sulfonation of benzene, 1,4-dichlorobenzene, toluene, and naphthalene were fully optimized using the M06-2X hybrid functional,[20] combined with the standard 6-311+G(2d,2p) basis set.[21,22] The M06-2X hybrid functional gives reliable energies for a variety of chemical applications.[23] As further validation of the theoretical results, the geometries of the critical structures along the reaction paths for the SO$_3$ sulfonation of benzene for processes in isolation, in noncomplexing and complexing solvents, were optimized at the SCS-MP2/6-311+G(2d,2p) *ab initio* level.[24] Harmonic vibrational frequency computations characterized the optimized structures. The zero-point vibrational energy corrections employed scaling factors of 0.967[25] for the M06-2X/6-311+G(2d,2p) and 0.951[26] for SCS-MP2/6-311+G(2d,2p). Intrinsic reaction coordinate (IRC) computations[27] of the transition structures verified the reactants, intermediates, and products on the PES. Bulk solvation effects were simulated by the IEFPCM method[28] (except for CFCl$_3$, where the Onsager treatment[29] was used). Cartesian coordinates and total energies for all optimized geometries are tabulated in the Supporting Information. All computations employed the Gaussian 09 program[30] and assumed 298.15 K as the standard temperature. H/D kinetic isotope effects (KIE's) were estimated theoretically following Skokov and Wheeler's[31] procedure (based on Bell's formulas).[32] The KIE values, deduced from energy and frequency computations for both C$_6$H$_6$ and 1,4-C$_6$H$_4$Cl$_2$ reactants (as well as their deuterated derivatives) in simulated nitromethane solvent for the rate-determining TS2 transition states of the stepwise mechanism, agreed well (see below) with the experimental data in nitromethane.[6,7,12]

Since the entropies of association and complexation are unfavorable, the free energies computed in isolation for the reactant complexes, explicit solvation complexes, etc. (see Tables 1−5) also are unfavorable (even though their enthalpies often are appreciably negative). The same is true for the computed energies and free energies when bulk solvation effects were simulated using the standard methods implemented in the Gaussian 09 program. However, such treatments do not estimate the free energy of association in solution suitably. Accurate modeling of such processes is hampered by the well-known, but hard to overcome, difficulties in estimating free energies for processes in solution theoretically (see, e.g., refs 33 and 34). When the partially compensating entropy contributions to $\Delta G$ for solute−solvent interactions are not considered, computations generally overestimate free energies in solution. Thus, "standard" (gas phase) estimates of the free energies of SO$_3$−nitromethane complexation give positive $\Delta G$ values (Table 4) due to the large entropy loss. But this disadvantage is expected to be far less in solution, where solvent molecules are readily available to interact with

**Table 2. Relative Energies and Free Energies (in kcal mol$^{-1}$, at 298.15 K) of Critical Structures along the Reaction Paths for the Sulfonation of Benzene (See Figure 2) and 1,4-Dichlorobenzene with Two SO$_3$'s in the Gas Phase and in Simulated CFCl$_3$ and CCl$_4$ Solutions (Concerted Mechanism) and in Simulated CH$_3$NO$_2$ Solution (Classic S$_E$Ar Mechanism) at M06-2X/6-311 +G(2d,2p)**

| | | benzene | | 1,4-dichlorobenzene | |
|---|---|---|---|---|---|
| | | $\Delta E$ | $\Delta G$ | $\Delta E$ | $\Delta G$ |
| gas phase[a] | reactant complex | −13.16 | 5.07 | −12.53 | 6.57 |
| | **TS** | **1.28** | **23.34** | **8.33** | **31.21** |
| | pyrosulfonic acid | −46.10 | −24.17 | −36.13 | −13.10 |
| CFCl$_3$ solvent[a,b] $\varepsilon$ = 2.0 | reactant complex | −13.29 | 4.83 | −12.55 | 6.57 |
| | **TS** | **-5.97** | **16.34** | **5.17** | **28.18** |
| | pyrosulfonic acid | −46.87 | −24.84 | −36.62 | −13.58 |
| CCl$_4$ solvent[a,c] $\varepsilon$ = 2.228 | reactant complex | −11.64 | 6.78 | −11.01 | 8.00 |
| | **TS** | **-3.01** | **19.38** | **5.71** | **28.76** |
| | pyrosulfonic acid | −45.65 | −23.81 | −35.38 | −12.46 |
| CH$_3$NO$_2$ solvent[a,c] $\varepsilon$ = 36.562 | reactant complex | −9.76 | 8.37 | −9.20 | 9.45 |
| | **TS1** | **-8.74** | **11.57** | **-3.10** | **18.78** |
| | $\sigma$ complex | −10.34 | 10.61 | −2.97 | 18.21 |
| | **TS2** | **-10.40** | **12.13 (12.63)[d]** | **0.76** | **23.79 (24.35)[d]** |
| | pyrosulfonic acid | −44.91 | −23.29 | −34.42 | −11.54 |

[a] Relative to benzene and two SO$_3$'s molecules. [b] Onsager model computations.[29] [c] IEF-PCM computations.[28] [d] Values for the deuterated isotopomers in parentheses. The KIE's were evaluated by employing eqs 1 and 2 in ref 31.

**Table 3. Relative Energies and Free Energies[a] (in kcal mol$^{-1}$, at 298.15 K) of Critical Structures for the Sulfonation of Benzene with Two SO$_3$'s in the Gas Phase and in Simulated CCl$_4$ and CH$_3$NO$_2$ Solutions (Concerted Mechanism; See Scheme 2) at SCS-MP2/6-311+G(2d,2p)**

| | gas phase | | CCl$_4$ solvent | | CH$_3$NO$_2$ solvent | |
|---|---|---|---|---|---|---|
| | $\Delta E$ | $\Delta G$ | $\Delta E$ | $\Delta G$ | $\Delta E$ | $\Delta G$ |
| reactant complex | −11.88 | 5.52 | −10.49 | 7.83 | −8.52 | 11.31 |
| TS | 14.33 | 36.19 | 10.45 | 33.72 | 3.62 | 28.86 |
| benzenepyrosulfonic acid | −28.73 | −7.71 | −30.69 | −7.74 | −29.86 | −5.55 |

[a] Relative to benzene and two separated SO$_3$ molecules.

solutes and products. Thus, it may be preferable to consider the relative energy ($\Delta E$) values of SO$_3$ complexation, rather than $\Delta G$ values based on gas phase computations.

## ■ RESULTS AND DISCUSSION

**Concerted Mechanism of Sulfonation with Sulfur Trioxide in Isolation and in Noncomplexing Solvents. The Nonexistence of a 1:1 Whelend Intermediate.** Our theoretical modeling of the inherent (i.e., uncatalyzed and noncomplexed) sulfonation with SO$_3$ in isolation (gas phase) or in simulated noncomplexing solvents (CCl$_4$, CFCl$_3$) revealed that the general mechanism followed an unexpected pathway. We first examined the reaction between a single SO$_3$ and benzene, which was too fast to be studied experimentally. Cerfontain's[6,7,11] first-order kinetics (in SO$_3$) were reported *only* for the sulfonation of the less reactive 1,4-dichlorbenzene in the noncomplexing CFCl$_3$ solvent. Contrary to expectations based in Scheme 1, only a concerted, single-step process was found. *No intermediate* of the Wheland type (or any other intermediate) in the key step could

be located at our DFT and correlated levels of theory. Instead, the *transition state* for this 1:1 process (Figure 1) involves near in-plane SO$_3$ attack concerted with simple, *direct* transfer of the ipso-H to the nearby SO$_3$ oxygen. However, the very high transition state energies both in the gas phase and in simulated CCl$_4$ and CFCl$_3$ solutions given in Table 1 rule out such processes, as they are inconsistent with the high rates of the experimental reaction at low temperatures (−20 °C or below).

Although Morley et al.[16] reported a putative toluene−SO$_3$ Wheland intermediate at the modest HF/4-31G/S* theoretical level (but did not give its structure details), they considered it "unlikely to occur under mild sufonation conditions" because of its high energy. We have searched for such an intermediate exhaustively but were only able to locate minima at HF levels in simulated polar media (but not in isolation at any level). This HF minimum starting geometry could not be reoptimized at a variety of DFT, MP2, and other correlated levels in simulated media or in the gas phase; dissociation occurred instead. Single point computations on the HF minimum geometry at all levels gave unrealistically high energies (in agreement with Morley et al.'s[16] findings). We also failed to locate a 1:1 SO$_3$-1,4-dichlorobenzene Wheland-type intermediate and, hence, were unable to verify Cerfontain's proposed mechanism (Scheme 1) (see ref 13). We are not able to account for Bosscher and Cerfontain's reported first-order kinetics in both 1,4-dichlorobenzene and SO$_3$ in CFCl$_3$ solution,[11] the unique example of such behavior we have found in the literature.

In addition to this 1:1 process (Table 1), Cerfontain's Scheme 1 considers the involvement of more than one sulfur trioxide in sulfonation reactions *in complexing* solvents[6,7,12] where second-order (in SO$_3$) kinetics and 2:1 consumed molar ratios of SO$_3$ to arene are observed experimentally. Our investigation provides further evidence for mechanisms involving the participation of two sulfur trioxide molecules in the rate-determining stage in isolation and in noncomplexing solvents. Morley et al.'s[16] Hartree−Fock theoretical study of toluene favored such a process, but solvation

**Table 4. Relative Energies and Free Energies (in kcal mol$^{-1}$, at 298.15 K) at M06-2X/6-311+G(2d,2p) for SO$_3$ Complexation with SO$_3$ and CH$_3$NO$_2$ in Isolation and in a Simulated CH$_3$NO$_2$ Solution**

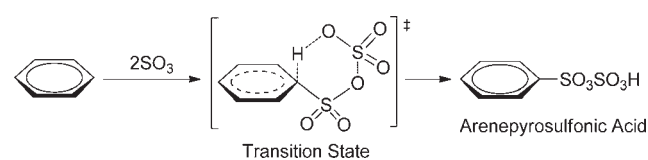| SO$_3$ complexes | gas phase | | CH$_3$NO$_2$ solvent | |
| --- | --- | --- | --- | --- |
| | $\Delta E$ | $\Delta G$ | $\Delta E$ | $\Delta G$ |
| SO$_3$···SO$_3$ (dimer) | −4.23 | 3.09 | −3.16 | 3.75 |
| CH$_3$NO$_2$···SO$_3$[a] | −8.22 | 1.59 | −8.23 | 2.58 |
| 2CH$_3$NO$_2$···SO$_3$[a] | −12.62 | 8.51 | −11.97 | 9.90 |
| CH$_3$NO$_2$···2SO$_3$[a,b] | −14.19 (−9.97)[d] | 6.25 (3.16)[d] | −13.46 (−10.30)[d] | 7.84 (4.09)[d] |
| 2CH$_3$NO$_2$···2SO$_3$[a,c] | −23.62 (−19.39)[d] | 8.93 (5.83)[d] | −18.62 (−15.46)[d] | 13.77 (10.03)[d] |

[a] Complexes with explicit CH$_3$NO$_2$ molecules. [b] Energy and free energy are relative to CH$_3$NO$_2$ and two separated SO$_3$'s. [c] Energy and free energy are relative to two CH$_3$NO$_2$ molecules and two separated SO$_3$'s. [d] Energy and free energy given in parentheses are relative to CH$_3$NO$_2$ and the (SO$_3$)$_2$ dimer.

**Table 5. Relative Energies and Free Energies (in kcal mol$^{-1}$, at 298.15 K) of Critical Structures for the Concerted Sulfonation Mechanism with Two SO$_3$'s of Benzene, Toluene, and Naphthalene in the Gas Phase and in Simulated CCl$_4$ Solution (Concerted Mechanism) at M06-2X/6-311+G(2d,2p)**

| compd, position of substitution | | gas phase | | CCl$_4$ solvent | |
| --- | --- | --- | --- | --- | --- |
| | | $\Delta E$ | $\Delta G$ | $\Delta E$ | $\Delta G$ |
| benzene | reactant complex | −13.16 | 5.07 | −11.64 | 6.78 |
| | **TS** | **1.28** | **23.34** | **-3.01** | **19.38** |
| | pyrosulfonic acid | −46.10 | −24.17 | −45.65 | −23.81 |
| toluene-2 | reactant complex | −14.64 | 5.36 | −13.06 | 7.05 |
| | **TS** | **-3.25** | **20.92** | **-7.33** | **17.14** |
| | pyrosulfonic acid | −46.60 | −22.26 | −45.93 | −21.58 |
| toluene-3 | reactant complex | −13.94 | 6.50 | −12.35 | 8.17 |
| | **TS** | **-0.33** | **23.29** | **-4.76** | **19.47** |
| | pyrosulfonic acid | −44.15 | −20.96 | −46.14 | −22.44 |
| toluene-4 | reactant complex | −13.80 | 6.66 | −12.02 | 8.91 |
| | **TS** | **-2.92** | **20.74** | **-8.59** | **15.38** |
| | pyrosulfonic acid | −46.96 | −23.08 | −46.43 | −22.43 |
| naphthalene-1 | reactant complex | −14.75 | 3.90 | −13.01 | 6.24 |
| | **TS** | **-4.30** | **18.71** | **-9.12** | **14.12** |
| | pyrosulfonic acid | −42.39 | −19.58 | −42.15 | −19.34 |
| naphthalene-2 | reactant complex | −13.76 | 4.57 | −12.45 | 5.45 |
| | **TS** | **-2.26** | **20.35** | **-7.08** | **16.26** |
| | pyrosulfonic acid | −46.72 | −23.95 | −46.13 | −23.36 |
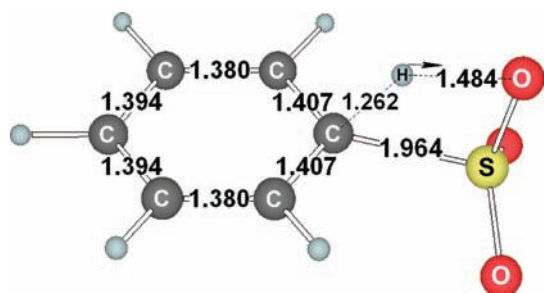


**Figure 1.** Computed transition structure ($C_s$ symmetry) for the S$_E$Ar sulfonation of benzene with a single SO$_3$ at M06-2X/6-311+G(2d,2p) in isolation (unsolvated).

**Scheme 2. Direct Mechanism of Sulfonation of Benzene with Two SO$_3$ Molecules in Isolation (Gas Phase) or in Nonpolar Media**



effects were not considered and only limited data were reported. Our findings at both M06−2X/6-311+G(2d,2p) and SCS-MP2/6-311+G(2d,2p) levels (Tables 2 and 3), which included forward and backward IRC checks of the optimized transition states (see Figure S3 of the Supporting Information), clearly establish a *concerted mechanism* for the reaction of two SO$_3$ molecules with arenes (benzene, toluene, naphthalene, and 1,4-dichlorobenzene) in isolation and in noncomplexing solvents. Onsager SCRS computations[29] modeled the CFCl$_3$ solvent (with M06−2X), while standard IEFPCM computations[28] were employed for CCl$_4$

19097

dx.doi.org/10.1021/ja201866h |*J. Am. Chem. Soc.* 2011, 133, 19094–19101
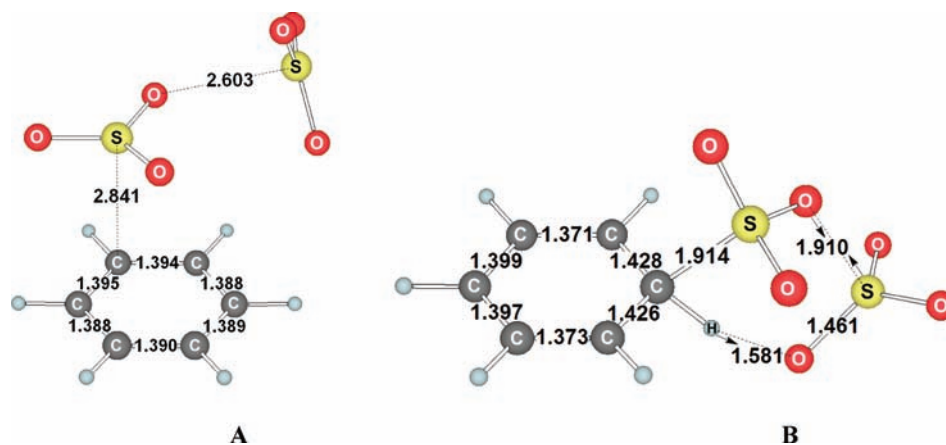
**Figure 2.** M06-2X/6-311+G(2d,2p) structures of (A) the reactant complex and (B) the transition state for the concerted $S_EAr$ sulfonation of benzene with two $SO_3$ molecules in isolation. (See Table 2 for data and Figure 4 for the structures in simulated $CH_3NO_2$ solution.)

simulations. In nice accord with experimental findings,[11] the resulting reaction barriers for sulfonation with two $SO_3$ molecules (Table 2) had much lower energies. The activation free energy for benzene in $CFCl_3$ was only 16.34 kcal/mol. As expected, all the computed reaction barriers for 1,4-dichlorobenzene are much higher than those for benzene.

At the suggestion of a reviewer, we also employed the SCS-MP2/6-311+G(2d,2p) level (as in Table 1) to compute data for the sulfonation of benzene with two $SO_3$'s in isolation and in simulated $CH_3NO_2$ (Table 3). Comparison with the M06-2X/6-311+G(2d,2p) findings (Table 2) confirms our most important conclusion: that the 2:1 sulfonation is much preferred energetically over the 1:1 alternative. The gas phase 1:1 MP2 TS free energy (48.51 kcal/mol Table 1) is over 12 kcal/mol higher than the 36.19 kcal/mol free energy for the 2:1 TS (Table 3). At SCS-MP2, the computed 1:1 concerted TS energy in simulated $CH_3NO_2$ (43.86 kcal/mol; Table 1) is 15.0 kcal/mol higher than the $\Delta G =$ 28.86 kcal/mol (Table 3) for the concerted 2:1 process.

However, there are significant differences in detail between the MP2 and M06-2X results. MP2 only follows the concerted mechanism (Scheme 2), both in the gas phase and in simulated $CH_3NO_2$ solution. As in Table 1 (for the 1:1 sulfonation), the M06-2X TS energies (Table 2) are lower than those at MP2 (Table 3) for the 2:1 process, but we note that adding the SCS correction to MP2 raises the TS energies by about 5—7 kcal/mol. Higher levels of theory are needed to decide whether MP2 or M06-2X provides more reliable results.

Since benzene reacts too rapidly, Cerfontain's[11] experimental sulfonation kinetics were measured on deactivated arene derivatives, such as 1,4-dichlorobenzene. Indeed, our theoretical TS energies of the latter are at least 7—8 kcal/mol higher than those for benzene (Table 2). Scheme 2 depicts the concerted mechanism of benzene sulfonation by two $SO_3$ molecules computed in isolation or in nonpolar solvents. This pathway is included in Figure 3.

The formation of $\pi$ (reactant) complex (A, Figure 2) is not included in Scheme 2, since it is unessential. Its positive free energy at 298.15 K is unfavorable at M06-2X/6-311+G(2d,2p) (Table 2). Contrary to Cerfontain's Scheme 1, *formation of a $\sigma$ complex intermediate* does not occur in isolation (gas phase). The sulfonation of benzene with two $SO_3$ molecules in the gas phase proceeds to a transition state (the M06-2X/6-311+G-(2d,2p) TS geometry is shown as B in Figure 2) and then directly

to the benzenepyrosulfonic acid product *without any intermediate* (Scheme 2). The TS structures for the arene sulfonations in simulated $CFCl_3$ and $CCl_4$ media, shown in the Supporting Information, are quite similar.[35]

In accord with Scheme 2, benzenepyrosulfonic acid was found to be the principal reaction product experimentally in the noncomplexing $CFCl_3$ solvent,[6,7,11] but it transforms further easily into other sulfonation derivatives (Scheme 1). Additional reactions are possible following the principal stage of the sulfonation[6,7,10] due to the reversible character of aromatic sulfonation and the high reactivity of reactants and products.[6,7] Thus, the arenepyrosulfonic acid may react with the arene to form arenesulfonic acid. Two arenepyrosulfonic acid molecules may form the anhydride of the arenepyrosulfonic acid and pyrosulfuric acid.[6,7,11]

**Mechanism of Sulfur Trioxide Sulfonation in Complexing Solvents.** The second-order kinetics (in $SO_3$) found experimentally by Cerfontain[6,7,12] for the sulfonation of 1,4-dichlorobenzene and several other arenes in complexing solvents (e.g., nitromethane and 1,4-dioxane) established the participation of two $SO_3$ molecules in the rate-controlling stage of sulfonation. Morley et al.'s[16] HF/4-31G/S* theoretical study suggested that two $SO_3$ molecules participate in the sulfonation of toluene, which starts from a toluene—$S_2O_6$ $\pi$ complex and proceeds via a Wheland intermediate to the pyrosulfonic acid product.

However, it is not clear how the two $SO_3$ molecules become involved. Our work shows that Cerfontain's interpretation (attack by a second $SO_3$ on a 1:1 Wheland intermediate; see Scheme 1) does not appear to be viable. Cerfontain discounted $(SO_3)_2$ dimer as a possible electrophile, since, as he stated, "A Raman spectral study has given evidence that, at concentrations of 10 mol % or less in solvents such as halogenated alkanes, sulfur trioxide is present mainly in its monomeric form."[36] Could the $SO_3$ dimer, stabilized relative to two $SO_3$ monomers in complexing solvents such as nitromethane, be a potential electrophile in such high dielectric media? Cerfontain's experimental rates of sulfonation in complexing solvents were considerably lower than those in noncomplexing solvents, despite the expected dielectric effect. Evidently, solvation stabilizes the $SO_3$ monomer or dimer reactants and inhibits reaction with the arene.

Table 4 shows that the energies ($\Delta E$) of complexation of a single $SO_3$ with one or two $CH_3NO_2$ molecules are appreciable. Although positive, the $\Delta G$ values probably are overestimated significantly. As discussed above, the free energies ($\Delta G$) for specific

solute—solvent complexation interactions, such as those between $SO_3$ and $CH_3NO_2$, are particularly hard to model accurately theoretically in bulk solvent media. Hence, it may be preferable to consider such association phenomena in terms of energy changes ($\Delta E$), even though these are not fully representative either. Since the dimerization and association energies (Table 4) of $SO_3$ are appreciable, their electrophilic sites may be blocked. The computed structures of the association complexes of $SO_3$ with $CH_3NO_2$ are shown in Figure S2 of the Supporting Information.
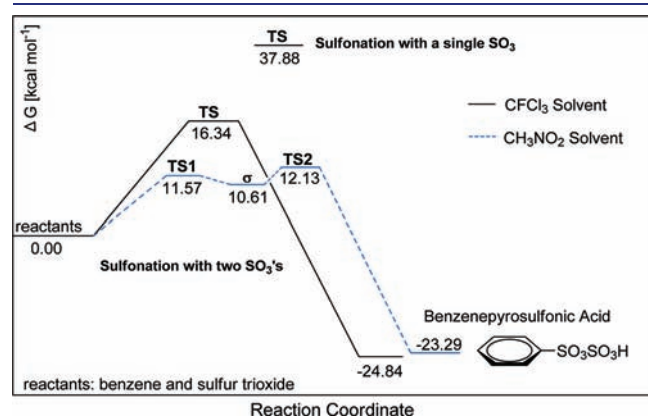


**Figure 3.** M06-2X/6-311+G(2d,2p) potential free energy surface profiles comparing the sulfonation of benzene with one $SO_3$ (unfavorable, concerted, in a simulated $CFCl_3$ medium; see Table 1) and the energetically more favorable alternative pathways with two $SO_3$'s (see Table 2). The concerted pathway for two $SO_3$'s in nonpolar $CFCl_3$ is contrasted with the stepwise $S_EAr$ pathway in the simulated highly polar $CH_3NO_2$. Note that the free energy profile of the latter does NOT take the explicit solvent complexation into account, because of the difficulties in modeling its free energies accurately in solution. Note the two important comparisons: (1) between one and two $SO_3$'s as well as (2) between the bulk solvent effects of $CFCl_3$ vs $CH_3NO_2$.

Our M06-2X/6-311+G(2d,2p) computations of the reaction of benzene with two $SO_3$ molecules failed to locate a Wheland-type *intermediate* in isolation. Instead, this model reaction is *concerted* in the gas phase and in noncomplexing solvents and proceeds via the *transition state* illustrated in Figure 2B. Notably, the barrier height (19.38 kcal mol$^{-1}$, $CCl_4$ solvent; Table 2) for this process is much lower than that ($\Delta G = 37.81$ kcal mol$^{-1}$) for the sulfonation with a single $SO_3$ molecule discussed earlier (see Table 1).

However, the complexing $CH_3NO_2$ solvent has a very large additional effect. The computational details for the sulfonation of benzene with two $SO_3$ molecules in the gas phase are quite different from those in simulated nitromethane solvent, which follows a *stepwise mechanism* with formation of a $ArH^+(SO_3)_2^-$ Wheland $\sigma$ complex intermediate in the first stage! Figure S4 depicts the results of IRC computations on the transition structures TS1 and TS2. Figure 4 shows their geometries and that of the Wheland-type $\sigma$ complex intermediate (see Table 2 for the energies). According to the NBO[37,38] charges, the aromatic ring of the $\sigma$ complex transfers 0.68 electron to the $(SO_3)_2$ moiety. The comparison of the benzene sulfonation energetics in noncomplexing solvent and in simulated $CH_3NO_2$ solution in Figure 3 emphasizes the remarkably large qualitative and quantitative effect of the polar medium. The $CH_3NO_2$ pathway is stepwise, and both TS's as well as the intermediate have greatly lowered energies. Experiment has shown that the sulfonation of benzene in $CH_3NO_2$ does not involve an intramolecular primary deuterium isotope effect.[5] This is consistent with the small elongation (and degree of breaking) of the ipso C—H bond in TS2 (to 1.184 Å, Figure 3). The theoretically computed[31,32] $k_H/k_D$ kinetic isotope effects (KIEs) for TS2 in simulated nitromethane, 1.01 (at 25 °C) for benzene and 1.02 (at 25 °C) for 1,4-dichlorobenzene, are in line with the secondary character of the experimental intramolecular KIE's for the sulfonation of both benzene ($k_H/k_D = 1.3 \pm 0.1$ at 20 °C)[5] and 1,4-dichlorobenzene ($k_H/k_D = 1.2 \pm 0.09$ at 20 °C)[7,12] in nitromethane.
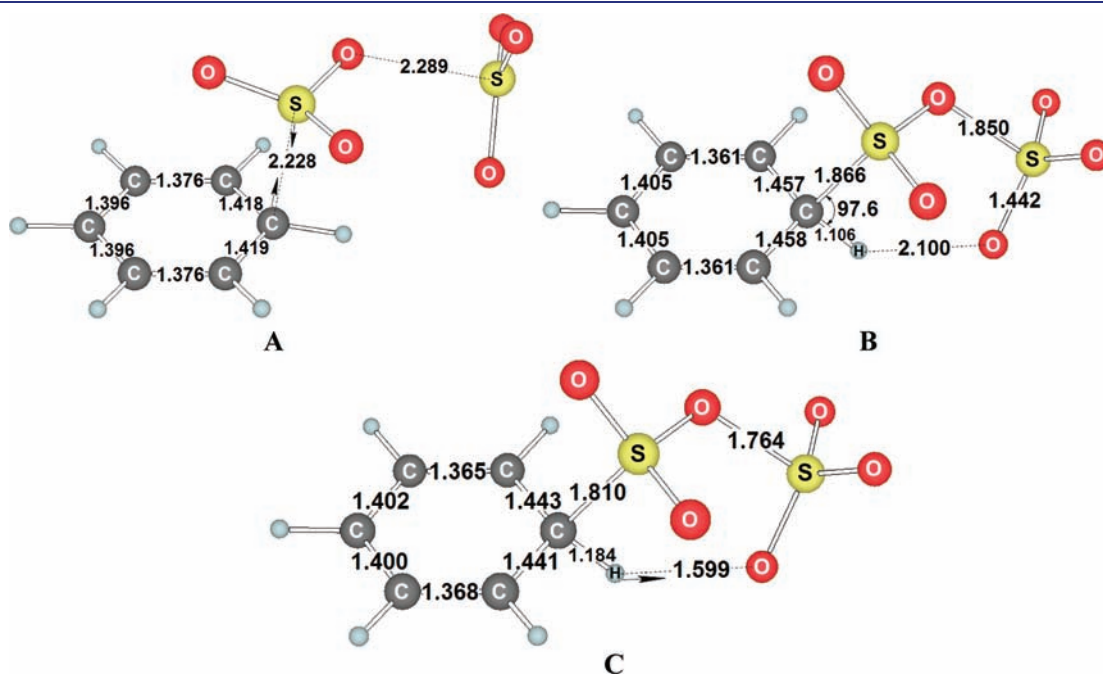


**Figure 4.** M06-2X/6-311+G(2d,2p) structures of (A) transition state TS1, (B) the $\sigma$ (Wheland-type) complex, and (C) TS2 for the $S_EAr$ sulfonation of benzene with the two $SO_3$'s in simulated $CH_3NO_2$ solvent. The total NBO charge of the benzene moiety of part B is +0.68.

19099

dx.doi.org/10.1021/ja201866h | *J. Am. Chem. Soc.* 2011, 133, 19094–19101

In contrast, the model reaction of a single $SO_3$ molecule with benzene in a simulated nitromethane medium (without explicit complexation) follows a *concerted* pathway (see the Supporting Information). Not only is the computed energy unrealistically high, but this process also does not correspond to the experimental kinetics, second-order in $SO_3$, for sulfonation of 1,4-dichlorobenzene in complexing solvents.[6,7,12] (Recall that the kinetic order could not be established experimentally for the sulfonation of benzene itself.)[11]

**Reactivity and Positional Selectivity.** Our theoretical energies and free energies for the sulfonation of benzene, toluene, and naphthalene with $SO_3$ in the gas phase and in simulated $CCl_4$ solution are presented in Table 5. Although all the TS energies for benzene substitution are about the same as those at the unactivated meta position of toluene, the ortho and para as well as both naphthalene positions have lower TS energies.

Methyl hyperconjugation facilitates *o*- and *p*-toluene substitution. In accord with experiment,[1,2] the 1-position of naphthalene is more reactive than the 2-position (due to better charge delocalization in the TS) even though the less crowded 2-sulfonic acid product is more stable.

Theory predicts 3—5 kcal mol$^{-1}$ lower activation energies in simulated $CCl_4$ media for all processes considered (Table 5), but the reactivity trends are the same as those in isolation.[35]

## CONCLUSIONS

We reiterate the refutations[7,16] of the traditional, widely disseminated "textbook-type" interpretations of aromatic sulfonation mechanisms depicting Wheland-type "$\sigma$ complex" arene intermediates with a single $SO_3$ molecule. Extending earlier studies on toluene,[15,16] our computations on benzene, toluene, naphthalene, and 1,4-dichlorobenzene reveal that the *inherent* (i.e., in the absence of a catalyst or in noncomplexing solvent) aromatic sulfonation mechanism with a single sulfur trioxide molecule is *concerted* and *does not* involve the conventional arenium nor any other 1:1 intermediate. However, the activation barriers for direct sulfonation with only a single $SO_3$ are much too high to account for the facile substitution or the 1:1 kinetics observed experimentally. Instead, we have shown that the participation of *two* $SO_3$ molecules rather than only one reduces the activation barrier considerably (by 12—20 kcal/mol), in good accord with the experimentally established kinetics (second-order in $SO_3$ for the reaction of 1,4-dichlorobenzene in complexing solvents) leading to arenepyrosulfonic acid products. While the sulfonation mechanism of benzene with two $SO_3$ molecules in nitromethane does follow the classic $S_EAr$ scheme involving a 2:1 $SO_3$—arene Wheland intermediate, direct sulfonation with two $SO_3$'s along a concerted pathway is rate-controlling in isolation and in noncomplexing solvents. Although the rate of sulfonation in complexing solvents (e.g., nitromethane) is reduced by the need to dissociate the $SO_3$—solvent aggregates, it is increased by the higher polarity of the medium. We agree with Cerfontain that arene sulfonation is in fact a far more complicated process than commonly realized. Further experimental and theoretical scrutiny is warranted to reconcile both approaches.

## ASSOCIATED CONTENT

**S** **Supporting Information.** Potential energy surface (PES) profiles for the sulfonation of benzene and of benzenesulfonic acid with a single $SO_3$; complete Gaussian 09 reference; optimized structures for $SO_3$ complexes with $SO_3$ and $CH_3NO_2$; IRC plots for the sulfonation of benzene with two $SO_3$'s in simulated $CFCl_3$ and $CH_3NO_2$ solutions; and energies, Cartesian coordinates, and structures of all optimized reactants, intermediates, transition states, and final products. This material is available free of charge via the Internet at http://pubs.acs.org.

## AUTHOR INFORMATION

### Corresponding Author
galabov@chem.uni-sofia.bg; schleyer@chem.uga.edu

## REFERENCES

(1) Smith, M. B.; March, J. *March's Advanced Organic Chemistry Reactions, Mechanisms and Structure*, 6th ed.; Wiley: New York, 2006; Chapter 11.

(2) Cerfontain, H. *Mechanistic Aspects of Aromatic Sulfonation and Desulfonation*; Wiley: New York, 1968.

(3) Gilbert, E. E. *Chem. Rev.* **1962**, *62*, 549–589.

(4) Gilbert, E. E. *Sulfonation and Related Reactions*; Interscience Publishers: New York, 1965.

(5) Bosscher, J. K.; Cerfontain, H. *J. Chem. Soc. B* **1968**, 1524–1526.

(6) Lammertsma, K.; Cerfontain, H. *J. Chem. Soc., Perkin Trans. 2* **1980**, 28–32.

(7) Cerfontain, H. *Recl. Trav. Chim. Pays-Bas* **1985**, *104*, 153–165.

(8) Cerfontain, H. J. A.; Schaasberg, Z. R. H.; Coombes, R. G.; Hadjigeorgion, P.; Tucker, G. P. *J. Chem. Soc., Perkin Trans. 2* **1985**, *5*, 659–667.

(9) Bochkareva, T. P.; Yakovlev, I. P.; Passet, B. V.; Sheiko, M. A. *J. Org. Chem. USSR (Engl. Transl.)* **1989**, 25, 1346–1450.

(10) Cremlyn, R. J. *Chlorosulfonic Acid: A Versatile Reagent*; The Royal Society of Chemistry: 2002.

(11) Bosscher, J. K.; Cerfontain., H. *Tetrahedron* **1968**, 24, 6543–6555.

(12) Bosscher, J. K.; Cerfontain, H. *Recl. Trav. Chim. Pays-Bas* **1968**, 87, 873–887.

(13) (a) In the 1985 review of his work,[7] Cerfontain stated, "The sulfonation of an arene by $SO_3$ in an aprotic solvent does, however, not proceed by the simple electrophilic two-step insertion mechanism, $ArH + SO_3 \rightleftharpoons ArH^+SO_3^- \rightarrow ArSO_3H$ still found in most organic chemistry textbooks but is a far more complicated process." (b) In 2002, Morley *et al.*'s[16] results "suggested that the Wheland intermediate $[ArH^+SO_3^-]$, which has been proposed as the key intermediate in many textbooks, is unlikely to be formed and it follows that the sulfonation process must follow some other path."

(14) Katritzky, A. R.; Kim, M. S.; Fedoseyenko, D.; Widyan, K.; Siskin, M.; Francisco, M. *Tetrahedron* **2009**, *65*, 1111–1114.

(15) Morley, J. O.; Roberts, D. W. *J. Org. Chem.* **1997**, *62*, 7358–7363.

(16) Morley, J. O.; Roberts, D. W.; Watson, S. P. *J. Chem. Soc., Perkin Trans. 2* **2002**, 538–542.

(17) Belen'kii, L. I.; Nesterov, I. D.; Chuvylkin, N. D. *Chem. Heterocycl. Compd. (Engl. Transl.)* **2006**, *42*, 1414–1420.

(18) Chuvylkin, N. D.; Nesterov, I. D.; Belen'kii, L. I. *Russ. Chem. Bull. Int. Ed.* **2007**, *56*, 1481–1486.

(19) As discussed below, free energies in solution, e.g., of $SO_3$ dimer complexes with $CH_3NO_2$ in the same solvent, are very difficult to compute reliably.[34] As we have no good way of doing so confidently, we interpret the energies (rather than the free energies).

19100

dx.doi.org/10.1021/ja201866h |*J. Am. Chem. Soc.* 2011, 133, 19094–19101

(20) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215–241.

(21) Curtiss, L. A.; McGrath, M. P.; Blaudeau, J. P.; Davis, N. E.; Binning, R. C., Jr.; Radom, L. *J. Chem. Phys.* **1995**, *103*, 6104–6113.

(22) Clark, T.; Chandrasekar, J.; Spitznagel, G. W.; Schleyer, P. v. R. *J. Comput. Chem.* **1983**, *4*, 294–301.

(23) (a) Zhao, Y.; Truhlar, D. G. *J. Phys. Chem. Lett.* **2008**, *112* 1095–1099. (b) Jacquemin, D.; Perpète, E. A.; Ciofini, I.; Adamo, C.; Valero, R.; Zhao, Y.; Truhlar, D. *J. Chem. Theory Comput.* **2010**, *6*, 2071–2085. (c) Zhao, Y.; Truhlar, D. G. *J. Chem. Theory Comput.* **2008**, *4*, 1849–1868. (d) Zhao, Y.; Truhlar, D. *Acc. Chem. Res.* **2008** *41* (2), 157–167.

(24) (a) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Molecular Orbital Theory*; Wiley: New York, 1986. (b) Grimme, S. *J. Chem. Phys.* **2003**, *118*, 9095–9102. (c) Grimme, S. *J. Comput. Chem.* **2003**, *24*, 1529–1537.

(25) Alecu, I. M.; Zheng, J.; Zhao, Y.; Truhlar, D. G. *J. Chem. Theory Comput.* **2010**, *6*, 2872–2887.

(26) Merrick, J. P.; Moran, D.; Radom, L. *J. Phys. Chem. A* **2007**, *111*, 11683–11700.

(27) (a) Fukui, K. *Acc. Chem. Res.* **1981**, *14*, 363–368. (b) Hratchian, H. P.; Schlegel, H. B. In *Theory and Applications of Computational Chemistry: The First 40 Years*; Dykstra, C. E., Frenking, G., Kim, K. S., Scuseria, G., Eds.; Elsevier: Amsterdam, 2005; pp 195–249.

(28) Tomasi, J.; Mennucci, B.; Cammi, R. *Chem. Rev.* **2005**, *105*, 2999–3093.

(29) (a) Kirkwood, J. G. *J. Chem. Phys.* **1934**, *2*, 351–361. (b) Onsager, L. *J. Am. Chem. Soc.* **1936**, *58*, 1486–1493. (c) Wong, M. W.; Frisch, M. J.; Wiberg, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 4776–4782. (d) Wong, M. W.; Wiberg, K. B.; Frisch, M. J. *J. Chem. Phys.* **1991**, *95*, 8991–8998. (e) Wong, M. W.; Wiberg, K. B.; Frisch, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 523–529. (f) Wong, M. W.; Wiberg, K. B.; Frisch, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 1645–1652.

(30) Frisch, M. J.; et al. *Gaussian 09*, Revision-A.02; Gaussian, Inc.: Wallingford, CT, 2009. See Supporting Information for full reference.

(31) Skokov, S.; Wheeler, R. A. *J. Phys. Chem. A* **1999**, *103*, 4261–4269.

(32) Bell, R. P. *Trans. Faraday Soc.* **1959**, *55*, 1–4.

(33) Singh, N.; Warshel, A. *Proteins* **2010**, 1705–1723.

(34) (a) Lelièvre, T.; Rousset, M.; Stoltz, G. *Free Energy Computations*; Imperial College Press: 2010. (b) Beierlein, F. R.; Michel, J.; Essex, J. W. *J. Phys. Chem. B* **2011**, *115*, 4911–4926 and references cited therein. (c) Beierlein, F. R.; Kneale, G. G.; Clark, T. *Biophys. J.* **2011**, *101*, 1130–1138 and references cited therein. (d) Knight, J. L.; Brooks, C. L. *J. Comput. Chem.* **2011**, *32*, 2909–2923.

(35) A reviewer asked if the concerted sulfonation process discussed in this section resembles a C–H insertion reaction. Instead, the geometry and other characteristics of the transition state for sulfonation in noncomplexing solvents differ considerably from those of typical C–H insertions. Note a related example: the benzene nitrosation, studied theoretically by Wheeler,[31] is such a C–H insertion process. Notably, its TS with a bridging H with its long and nearly equal 1.35 Å (CN) and 1.38 Å (C–H) distances (see Figure 4 in ref 31.) and the very large kinetic H/D isotope effect of 11.5 are very different from the corresponding sulfonation characteristics.

(36) (a) Gillespie, R. J.; Robinson, E. A. *Can. J. Chem.* **1961**, *39*, 2189–2200. (b) Gillespie, R. J.; Robinson, E. A. *Can. J. Chem.* **1962**, *40*, 658–674.

(37) Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 735–746.

(38) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899–926.