NMR Characterization of Sulfonation Products of Phenylchloroformate with Verification of NOE Effects by Molecular Modeling

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In the trial scale-up of the sulfonation of phenylchloroformate and subsequent formation of sulfonated phenyl carbonates, samples from the batch process showed a number of unexpected by-products. Because they were suspected to have an unusual ring substitution pattern, phenylchloroformate sulfonation was studied by ^{1}H and two-dimensional nuclear magnetic resonance (NMR) techniques. Distance geometry was used to compute internuclear distances, which were used to substantiate the observation of the nuclear Overhauser effect. The reaction mechanism leading to these by-products is proposed.

Index Headings: **Phenylchloroformate; Sulfonation; ^{1}H NMR; Two-dimensional NMR; Potential energy computation.**

INTRODUCTION

Aromatic sulfonation has great synthetic importance and has been reviewed extensively in the literature.[1-3] It is also a process of significant industrial relevance, particularly in the production of anionic surfactants.[4] Unilever has specific interest in various sulfonated phenyl carbonates, and a process was developed to prepare these carbonates from 4-sulfophenylchloroformate.[5] The trial scale-up process to synthesize large quantities of 4-sulfophenylchloroformate and the subsequent desired carbonate revealed a mass imbalance due to the presence of by-products ($\leq$3.0%) that were not encountered in the earlier laboratory preparations. In order to eliminate these unwanted contaminants and optimize the yield, it became necessary to make structural identifications of these reaction by-products.

It had been speculated that the presence of water in the batch process might have been responsible for these degradation products. Since hydrolysis of chloroformates results in the corresponding alcohol derivative, it was hypothesized that the by-products were most likely a mixture of sulfonated phenols and sulfonated diphenylcarbonates. The synthesis of these postulated by-products was undertaken in order to verify their chemical structures. One particular synthetic scheme resulted in a mixture of sulfonated species (sample A) that was difficult to separate and purify. High-performance liquid chromatography (HPLC) analysis of sample A revealed a combination of materials similar to the by-product mixture from the large-scale production sample. Mass spectrometry (MS) confirmed the presence of a mixture of materials and identified four major products. ^{1}H and two-dimensional (2D) nuclear magnetic resonance (NMR) were used to determine the structures of the components of this mixture and therefore identify the individual by-product components of the large-scale batch process of the desired sulfonated phenyl carbonate.

EXPERIMENTAL

Preparation. *Disodium 4-Hydroxybenzene-1,3-Disulfonate.* To a solution of 14.1 g of oleum (30% SO_3 in H_2SO_4) chilled in an ice bath was added 5.0 g (0.053 mol) of phenol. The reaction mixture was stirred and heated at 100°C. After 4 h, ^{1}H NMR of the reaction mixture in D_2O indicated the presence of >90% disulfonated product. The reaction mixture was then chilled in an ice bath, and water was slowly added to the acidic mixture. Finally, the solution was neutralized with Na_2CO_3 and the mixture was lyophilized. The resulting white solid was analyzed by ^{1}H NMR and was found to contain ~90% of the disulfonated phenol, disodium 4-hydroxybenzene-1,3-disulfonate, and <10% of the monosulfonated phenol, sodium 4-hydroxybenzenesulfonate.

Trisodium (2,4-Disulfophenyl)(4'-Sulfophenyl)Carbonate. To a solution of 0.2 g (0.005 mol) of NaOH in 30 mL of H_2O was added 2.0 g (0.0067 mol) of disodium 4-hydroxyphenyl-1,3-disulfonate. To this stirring basic solution (pH = 11.7) was added slowly 1.20 g (0.0044 mol) of 4-sulfophenylchloroformate as a solid. During the addition, HCl is liberated and the pH of the solution decreases. The pH was maintained at 6.5–7.0 during the addition of the chloroformate with a 2N NaOH solution. After addition was complete, the pH of the solution was lowered to 4.0 with HCl to prevent further decomposition of the carbonate. This aqueous solution was then lyophilized, producing a white powder (sample A). Both HPLC and NMR experiments showed this product to be a mixture of four materials, with the major product being the

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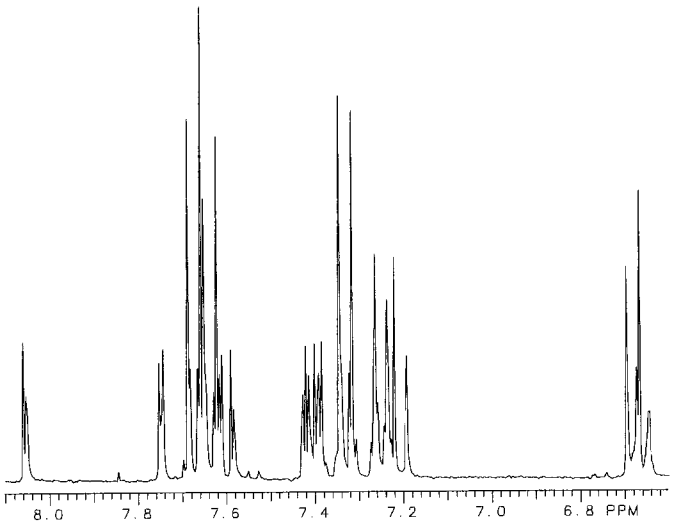


FIG. 1. ^{1}H NMR spectrum of sample **A**, containing 4-hydroxybenzenesulfonic acid (**A1**); 4-hydroxybenzene-1,3-disulfonic acid (**A2**); (2,4-disulfophenyl)(4′-sulfophenyl)carbonate (**A3**); and bis(4-sulfophenyl) carbonate (**A4**).

desired trisodium (2,4-disulfophenyl)(4′-sulfophenyl) carbonate.

NMR Spectroscopy. The NMR experiments were performed on a Varian XL-300 NMR spectrometer. A 5-mm ^{1}H/broad-band switchable probe was used.

Proton Spectrum. The proton 90° pulse was 20 μs. Typical conditions were: block size 32k and 500 scans. The spectral width was 4000 Hz.

2D Homonuclear Correlated Spectra. DQF-COSY (double quantum filtered COSY)[6] and NOESY (nuclear Overhauser enhancement spectroscopy)[7] were recorded with 1k × 1k data points in the t_2 and t_1 dimensions, respectively. Both experiments were recorded in pure phase mode by using the TPPI (time proportional phase incrementation)[8] technique. A mixing time of 200 ms was used in the NOESY experiment.

Minimum Energy Conformation Computations. Sybyl Molecular Modeling software (Tripos Associates) was used to generate minimum energy conformations of the desired structure. Conformations were generated with the use of macros developed at Unilever Research U.S. for automating the process of generating low-energy geometries through dynamic annealing. The macro submitted the structure for a series of 10 dynamic annealing experiments, taking the last point in one dynamics run as the starting point for the next. The setup conditions for each dynamic annealing study were as follows: the temperature was increased from 300 K to 2000 K in 500 K steps with a simulation time of 500 femtoseconds (fs) for each step. The system was held at 2000 K for 10 picoseconds (ps) and slowly cooled in 250 K steps down to 300 K with a simulation time of 1 ps/step. The time-step was set to 1 fs, and data were stored every 5 fs. Each structure obtained was minimized with the use of the TRIPOS force field[9] with the Powell minimization method.[10] The Gasteiger–Huckel method[11] was used for applying atom centered charges. The 10 structures were compared, and the lowest energy structure was used to obtain distance measurements.

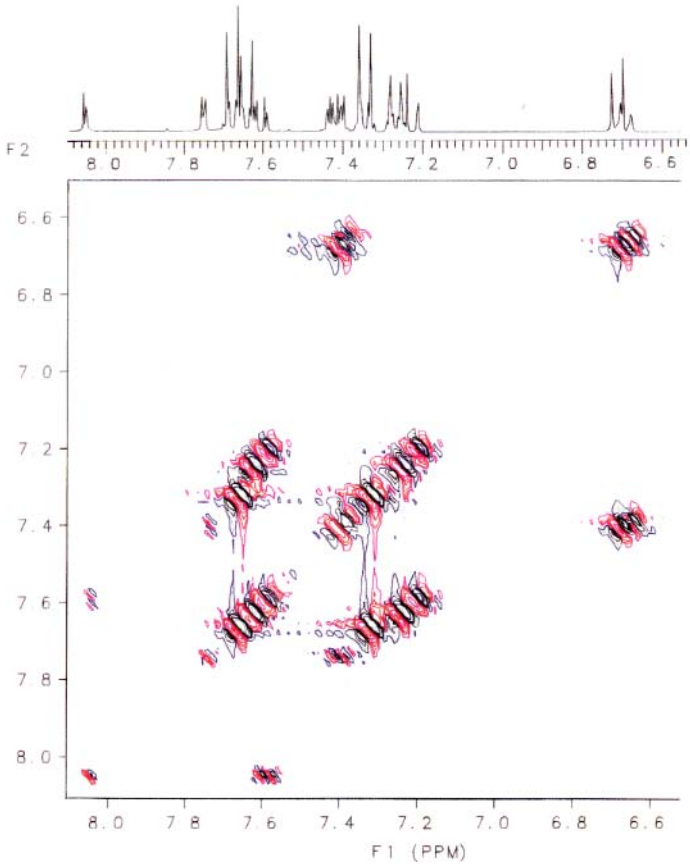


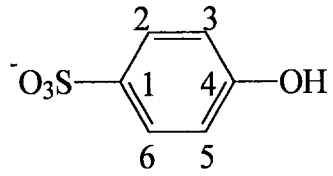
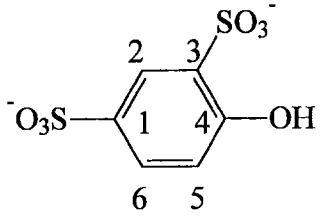
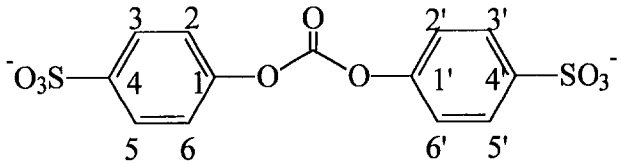
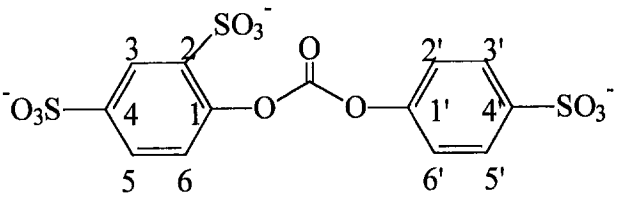
FIG. 2. Phase-sensitive DQF-COSY contour plot of sample **A**, containing 4-hydroxybenzenesulfonic acid (**A1**), 4-hydroxybenzene-1,3-disulfonic acid (**A2**); (2,4-disulfophenyl)(4′-sulfophenyl)carbonate (**A3**); and bis(4-sulfophenyl)carbonate (**A4**).

RESULTS AND DISCUSSION

NMR Spectroscopy. The strategy of the NMR analysis was to first establish the *J*-coupling network by homonuclear correlation spectroscopy. This would separate the ^{1}H frequencies into signal sets, each of which would then be correlated to the corresponding aromatic rings in the mixture. ^{1}H NMR was used because the coupling constants readily reveal the ring substitution patterns, thereby allowing the structure of the positional isomers to be ascertained. Since all the suspected molecules have sulfonated aromatic rings, their similar chemical environments resulted in a ^{1}H spectrum that has complicated features crowded within 1.5 ppm in the aromatic region (Fig. 1). Lack of resolution on its COSY plot did not permit the establishment of bond connectivities. For this reason, phase-sensitive double quantum filtered COSY was used instead (Fig. 2).

On the basis of DQF-COSY data, five signal sets corresponding to five *J*-coupling networks were established. Together with their chemical shifts, these are listed in Table I. Set 1 is a pair of *o*-doublets, evidence of a 1,4-disubstituted aromatic ring. Set 2 has an *o*-doublet, a pair of *o*/*m*-doublets, and an *m*-doublet. These are indicative of a 1,2,4-trisubstituted aromatic ring. Both set 3 and set 4 have an *o*-doublet, revealing both to be a 1,4-disubstituted aromatic ring. Set 5 has an *o*-doublet, a pair of *o*/*m*-doublets, and an *m*-doublet, demonstrating the presence of a second 1,2,4-trisubstituted aromatic ring.

TABLE I. Frequency assignments of mixture A in D_2O at 298K (in ppm downfield from TSP).

Molecule	Coupling Pattern	δ	Assignments
	Set 1		
	o-doublet	6.662	H3,H5
	o-doublet	7.399	H2,H6
	Set 2		
	o-doublet	6.683	H5
	o/m-doublets	7.411	H6
	m-doublet	7.749	H2
	Set 3		
	o-doublet	7.331	H2,H6,H2',H6'
	o-doublet	7.674	H3,H5,H3',H5'
	Set 4		
	o-doublet	7.252	H2',H6'
	o-doublet	7.638	H3',H5'
	Set 5		
	o-doublet	7.208	H6
	o/m-doublets	7.600	H5
	o-doublet	8.055	H3

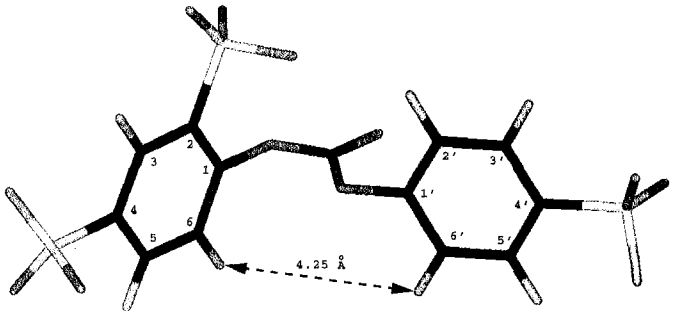


FIG. 3. Low-energy conformation of tri-sodium (2,4-disulfophenyl)(4′-sulfophenyl) carbonate by molecular modeling.

A sample of sodium 4-hydroxybenzenesulfonate was obtained from a commercial source (Eastman Kodak). With the use of this as a standard, set 1 was identified as 4-hydroxybenzenesulfonic acid (**A1**). On the basis of the relative shielding effects of the hydroxyl and sulfonate groups, the high-field doublet at 6.662 ppm was assigned to the proton (H3) *ortho* to the hydroxyl group, and the low-field doublet at 7.399 ppm to the proton (H2) *ortho* to the sulfonate group. Set 2 indicates a trisubstituted ring. Therefore it can be assigned to either 4-hydroxybenzene-1,3-disulfonic acid (**A2**) or the disulfonated ring of (2,4-disulfophenyl)(4′-sulfophenyl)carbonate (**A3**). Between these two rings, the hydroxy group renders more shielding at the *ortho* position than the carbonate group. Indeed, the *o*-doublet at 6.683 ppm is close to the *o*-doublet at 6.662 ppm in set 1. Since in set 1, the line at 6.662 ppm has been assigned to the proton *ortho* to the hydroxy group, the line at 6.683 ppm in set 2 is therefore likely to be a proton *ortho* to a hydroxy group rather than a carbonate group. Set 2 is therefore assigned to **A2** with H2, H5, and H6 assigned according to their expected coupling patterns. Set 5 is then assigned to the disulfonated ring of **A3**.

Set 3 and set 4 are both *o*-doublets which come from *p*-disubstituted rings. Either doublet may be assigned to bis(4-sulfophenyl)carbonate (**A4**) or to the monosulfonated ring of **A3**. There is no *a priori* criterion for assigning these two sets to either species. However, the signal intensity of either set of nonequivalent protons (H2′ + H6′ or H3′ + H5′) in the monosulfonated ring of **A3** is expected to be twice that of any proton on the disulfonated ring of the same molecule. On the basis of intensity consideration, set 4 was assigned to the monosulfonated ring of **A3** and set 3 to **A4**. On the basis of the relatively stronger shielding effect of the carbonate group compared with the sulfonate group, the high-field doublets in these two sets are assigned to the protons *ortho* to the carbonate and the low-field doublets to the protons *ortho* to the sulfonate.

It remains to be proven whether the mono- and disulfonated rings are linked by a carbonate group to form **A3**. Since the two closest protons on these two rings are separated by eight bonds, long-range coupling through bonds cannot be observed. On the other hand, its conformation may allow the two rings to come close to each other so that some of the protons on the two rings undergo cross-relaxation due to through-space dipolar coupling (i.e., nuclear Overhauser effect[12]) with each other. In a

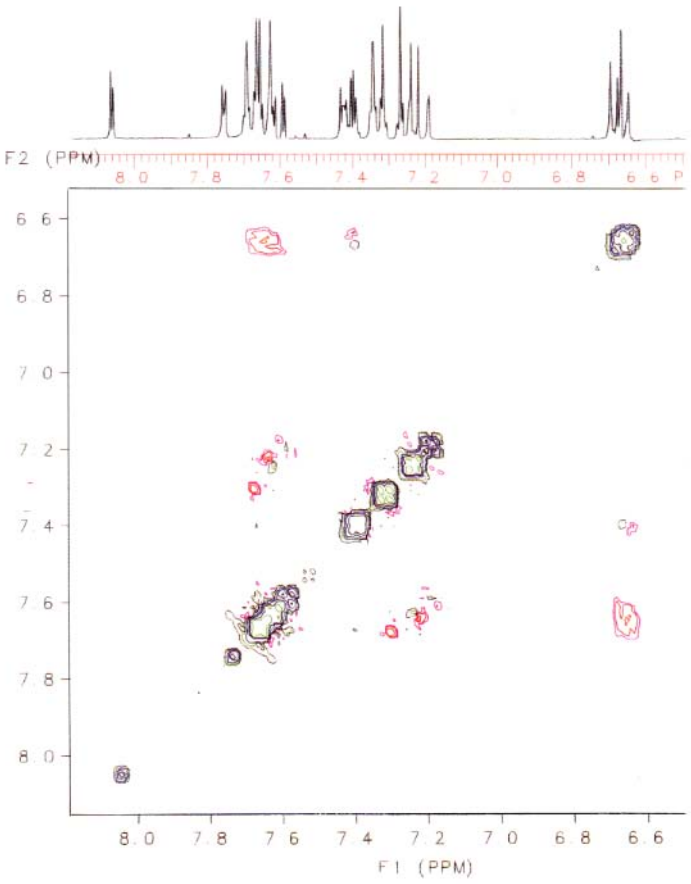


FIG. 4. Phase-sensitive NOESY contour plot of sample **A**, containing 4-hydroxybenzenesulfonic acid (**A1**); 4-hydroxybenzene-1,3-disulfonic acid (**A2**); (2,4-disulfophenyl)(4′-sulfophenyl)carbonate (**A3**); and bis (4-sulfophenyl)carbonate (**A4**).

2D NMR NOESY experiment, such interactions can be observed as cross-peaks on a contour plot. Because NOE is inversely proportional to (r_{ij}^6),[13] where r is the distance between a pair of protons (i, j) that cross-relax each other, the cross-peak intensity falls off rapidly as a function of internuclear distance. It became necessary to identify the upper limit for internuclear distance for observable NOEs. Calculation based on a simple uniform-averaging model estimated that NOEs corresponding to $r_{ij} \leq 5.0$ Å should be observable.[14]

In order to gain some insight into whether there are NOEs between pairs of protons on the two rings of (2,4-disulfophenyl)(4′-sulfophenyl)carbonate, a molecular model for this species was constructed with the use of the Tripos force field.[10] After minimization of its potential energy, internuclear distances were computed for the resultant molecular conformation (Fig. 3). Among the pairs of protons on separate rings, only H6–H2′ has an internuclear distance of 4.25 Å, which is under the 5.0-Å upper limit for observable NOE. Since all other inter-ring ^{1}H–^{1}H distances exceed the 5.0-Å limit, corresponding NOEs would not be expected.

Other than the several cross-peaks due to proton pairs on the same ring, the only cross-peak present in the NOESY contour plot (Fig. 4) due to a proton pair on separate rings is that of H6–H2′. This observation verifies that the two rings are indeed linked as one molecule. Since the

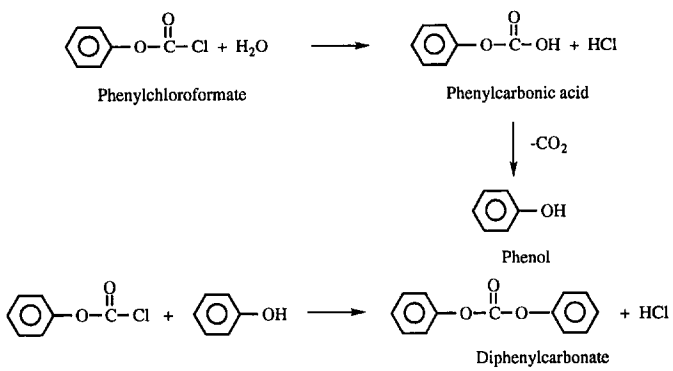


FIG. 5. Reaction scheme of the initial hydrolysis and condensation reactions of phenylchloroformate.

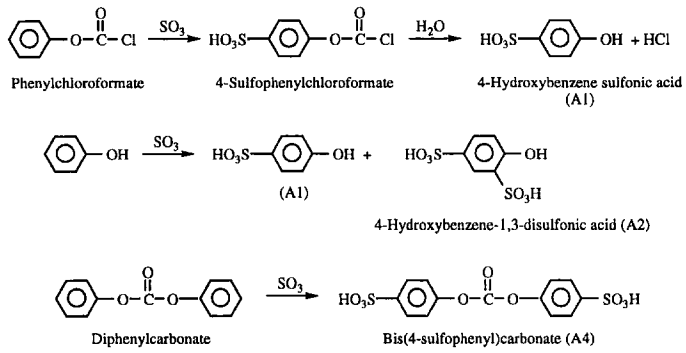


FIG. 6. Reaction scheme of the sulfonation of phenylchloroformate, phenol, and diphenylcarbonate.

chemical shifts of the two protons (H6 at 7.208 ppm and H2′ at 7.252 ppm) *ortho* to the bridging group are similar to that of the *ortho* protons (H2 and H2′ both at 7.331 ppm) in **A4**, the bridging group responsible for rendering similar shielding at the *ortho* positions is therefore likely to be a carbonate. Hence the structure of **A3** is postulated.

Reaction Mechanisms. Sulfonation of phenol and aromatic compounds in general has been studied extensively by Cerfontain and co-workers.[15–19] Depending upon the nature of the solvent, the reaction conditions, and the substituent on the aromatic ring, the sulfonation site can be varied. Phenols and aryl carbonates undergo *ortho* and *para* substitution with *para* substitution being preferred primarily because of steric considerations.[20] Monosulfonation occurs quite readily to activated aromatic rings, such as phenol and aryl carbonates, but disulfonation is more difficult because the addition of an electron-withdrawing sulfonate group makes the aromatic ring less susceptible to the electrophilic attack of another sulfonate. Phenol will undergo disulfonation in the presence of excess reactant, but since carbonate is not as strong an activating group as hydroxy and since there is steric hinderance blocking the *ortho* positions of the carbonate, little if any disulfonation occurs. Because both the by-product mixture of the carbonate scale-up reaction and sample **A** contain mono- and disulfonated phenols (**A1** and **A2**), and diphenylcarbonates with mono- and disulfonated aromatic rings (**A3** with monosulfonated aromatic rings and **A4** with mono- and disulfonated aromatic rings), a reaction mechanism has been proposed to explain the presence of this unusual mixture of sulfonated aromatic compounds. The product from the scale-up preparation of the desired sulfonated phenyl carbonate formed by reaction of 4-sulfophenylchloroformate and an alcohol was analyzed by HPLC. The chromatogram revealed >97% of the desired 4-sulfophenylcarbonate along with four main anionic contaminants. These anionic by-products were proposed to result from minor hydrolysis of the phenylchloroformate, which is more difficult to control on a commercial scale than on the laboratory scale. Hydrolysis of chloroformates forms carbonic acids which undergo decarboxylation to form the corresponding alcohols. For phenylchloroformate, the phenol produced from hydrolysis can then react with the large excess of phenylchloroformate present to produce diphenylcarbonate (Fig. 5). While phenols are relatively unreactive toward chloroformates at room temperature, this reaction could be catalyzed by metal impurities present in the mixture and the storage and transport vessels utilized.[21] It is actually this mixture—phenylchloroformate, phenol, and diphenylcarbonate—which was then subjected to sulfur trioxide sulfonation.

During the sulfonation reaction, the major reactant, phenylchloroformate, is sulfonated in the *para* position to form the desired 4-sulfophenylchloroformate (Fig. 6). Even in the presence of excess SO_3, only the monosubstituted 4-sulfophenylchloroformate is isolated. The two hydrolysis products, phenol and diphenylcarbonate, also undergo sulfonation to produce 4-hydroxybenzenesulfonic acid (**A1**), 4-hydroxybenzene-1,3-sulfonic acid (**A2**), and bis(4-sulfophenyl) carbonate (**A4**) (Fig. 6). The phenol undergoes both mono- and disulfonation in the *ortho* and *para* positions in the presence of excess SO_3, while the diphenylcarbonate undergoes only monosubstitution on both phenyl rings in the *para* position. Diphenylcarbonate was subjected to a large excess of SO_3 and elevated temperatures in model reactions to force further sulfonation of the aromatic rings, but only **A4** was isolated. Finally, any moisture present in the reaction vessel after sulfonation is complete will cause hydrolysis of 4-sulfophenylchloroformate to form **A1**. This process explains the presence of three of the four by-products, **A1**, **A2**, and **A4**.

The final reaction sequence responsible for the carbonate by-products is the reaction of the sulfonated phenols (**A1** and **A2**) present in the mixture with the 4-sulfophenylchloroformate, as shown in Fig. 7. While this reaction is relatively slow, it is catalyzed by both metal impurities and quaternary ammonium salts, which are present in the final step of the reaction to form the desired carbonate.[21,22] This reaction sequence explains the presence of the remaining identified by-product, (2,4-disulfophenyl)(4′-sulfophenyl)carbonate (**A3**) and **A4**. **A3** could not have come from direct sulfonation of diphenylcarbonate since, as previously mentioned, diphenylcarbonate will only undergo sulfonation in the two aromatic *para* positions to form **A4** (Fig. 6).

This reaction mechanism explains the presence of the by-products found in the large-scale production of the

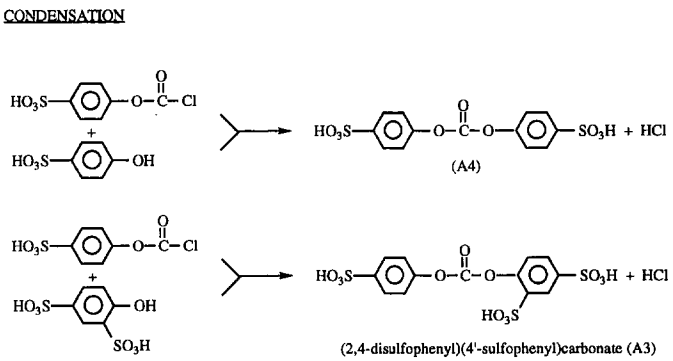


FIG. 7. Reaction scheme of the condensation of 4-sulfophenylchloroformate and mono- and disulfonated phenols.

desired sulfonated phenyl carbonate, and the same reaction mechanism is responsible for the combination of materials in sample A that was analyzed by the various NMR methods. Sample A was the reaction mixture from the synthesis of trisodium (2,4-disulfophenyl)(4'-sulfophenyl)carbonate, which required the use of an aqueous medium to perform the condensation reaction between disodium 4-hydroxybenzene-1,3-disulfonate, and 4-sulfophenylchloroformate because of the solubility limits of the sulfonated reactants.[21] The presence of the aqueous solvent causes some hydrolysis of the 4-sulfophenylchloroformate to produce **A1**, which then condenses with 4-sulfophenylchloroformate to produce **A4**, along with unreacted sulfonated phenols. Thus the reaction product mixture for sample A contains the same four compounds as the by-product mixture from the large-scale process of the carbonate product.

CONCLUSION

The four sulfonated species—4-hydroxybenzenesulfonic acid (**A1**), 4-hydroxybenzene-1,3-disulfonic acid (**A2**), bis(4-sulfophenyl)carbonate (**A3**), and (2,4-disulfophenyl)(4'-sulfophenyl)carbonate (**A4**)—were synthesized and characterized by NMR and MS. This information was used in a HPLC analysis to confirm their presence in the large-scale sulfonation of phenylchloroformate. A reaction mechanism explaining the formation of these by-products in the large-scale process was proposed, and hydrolysis of the major starting material, phenylchloroformate, is therefore responsible for the impurities in the final carbonate product. While hydrolysis side reactions were known to be a problem, a marked improvement in the quality of the desired product in the batch process coincided with increased measures to keep the conditions as dry as possible.

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