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Acid-catalyzed transfer sulfonation of anisole using overcrowded polymethylbenzenesulfonic acids^{*,†}

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Abstract. Transfer sulfonations of anisole using various polymethylbenzenesulfonic acids (PoMBR's) catalyzed by trifluoromethanesulfonic acid at 25°C are described. The observed reactivity order for transfer sulfonation increases in the order 2,4-DiMBS, 2,6-DiMBS, 2,3,4,5-TeMBS (all non-reactive) < 2,3,5,6-TeMBS \approx 2,4,6-TrMBS < 2,3,4,6-TeMBS < PeMBS. This order illustrates that the main factor in determining the transfer sulfonation reactivity is – in addition to the electronic activation by the 4-methyl – the degree of overcrowding around the sulfonic acid group of the PoMBS. A mechanism is suggested in which the essential step involves the transfer of SO_3H^+ from the 1-arenonium-1-sulfonic acid ion to the anisole.

Introduction

Electrophilic aromatic sulfonation¹ is conveniently carried out using sulfur trioxide² and the derived Brönsted acids sulfuric acid³, fuming sulfuric acid³, chlorosulfuric acid^{4,5}, methane- and benzenepyrosulfonic acid⁵ and acetyl sulfuric acid⁶. With the protic acids, the reactive sulfonating entity is in general of the BSO_3H structure which transfers SO_3H^+ to the aromatic substrate. This type of reaction is in fact sensitive to acid catalysis, since the sulfonation rate coefficient of, for example, the entity $\text{H}_3\text{S}_2\text{O}_7^+$ in weak oleum is very much higher than that of the species $\text{H}_2\text{S}_2\text{O}_7$ in highly concentrated aqueous sulfuric acid³.

Sulfo-group migrations have been observed in the field of arenesulfonic acid isomerization. They are acid-catalyzed and, in sulfuric acid as solvent, they proceed generally intermolecularly via protiodesulfonation and subsequent sulfo-deprotonation⁸. High-temperature transfer sulfonations⁹ are evident from the formation of sulfanilic acid and 2-methylphenol, upon heating a mixture of anilinium chloride and 2-methylphenol-4-sulfonic acid¹⁰, and from the formation of 1,4-benzenedi-, 2,6-naphthalenedi- and 4,4'-diphenyldisulfonates from the corresponding monosulfonates in the presence of Hg or Cr as catalyst¹¹. Further, it was proposed that transfer sulfonation plays a role in the formation of symmetrical sulfones upon reaction of simple aromatic hydrocarbons with dissimilar arenesulfonic acids at high temperature¹².

Electrophilic aromatic transfer substitutions are of general occurrence and have been observed in nitration¹³, alkylation^{14,15}, acylation^{16,17} and sulfonylation¹⁸. As is apparent in a number of these studies, the transfer substitution using overcrowded reagents proceeds more rapidly when the relief of steric strain is larger. We now report on the low-temperature transfer sulfonation of anisole with a series of polymethylbenzenesulfonic acids (PoMBS's). These reactions require acid catalysis for which trifluoromethanesulfonic acid^{18,19} proved convenient.

Results and discussion

Upon addition of 2.0 mmol of $\text{CF}_3\text{SO}_3\text{H}$ at 25°C to a mixture of 1.0 mmol of 2,4,6-trimethylbenzenesulfonic acid (2,4,6-TrMBS) dihydrate and 3.0 mmol of anisole, there resulted a homogeneous solution. After 115 h, the sulfo transfer from 2,4,6-TrMBS to the anisole was found to be 91%. Both *o*- and *p*-anisolesulfonic acid were formed in a ratio of 0.13. Upon dissolving 1.0 mmol 2,4,6-TrMBS dihydrate in 11.0 mmol of $\text{CF}_3\text{SO}_3\text{H}$, the relative content of 1,3,5-TrMB appeared to be less than its limit of ^1H NMR detection which is 2%.

Relative rates of transfer sulfonation of anisole by PoMBS's have been determined using deficient amounts of the corresponding potassium sulfonates (Table I). Under the chosen reaction conditions, no disturbing side-reactions, such as demethylation and sulfonylation of anisole, take place²⁰, although protonation of the phenyl ring of both anisole and the PoMBS's is apparent from the ^1H NMR spectra. The amount of converted PoMBS is equal to the amount of anisolesulfonic acid formed. The reactions were found to be first order with respect to the PoMBS for conversions up to – in general – three half-lives. The first-order

* Dedicated to Prof. W. Drenth on the occasion of his retirement from the chair of Physical Organic Chemistry at the University of Utrecht.

† Aromatic sulfonation 109. For part 108, see H. Cerfontain and A. Koeberg-Telder, *Phosphorus, Sulfur and Silicon* 42, 223 (1989).

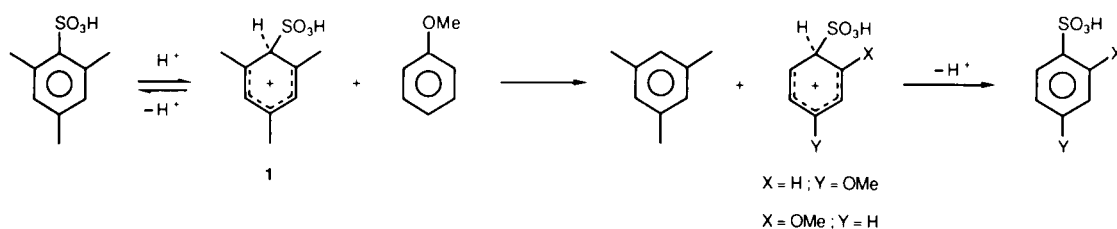
Table 1 Transfer sulfonation of anisole (3.0 mmol) by polymethylbenzenesulfonates, using $\text{CF}_3\text{SO}_3\text{H}$ (2.0 mmol) as catalyst at 25 °C.

PoMBS ^a	Method ^b	Reaction time (h) ^c	Reaction mixture composition (%) ^d							10 ⁴ · psk ₁ (ks ⁻¹)
			PoMBS	PoMB + HS ^e	PoMB	PoMB + H ^e	PhOMe ^f	Ph + HOMe ^e	MeOC ₆ H ₄ S ^g	
2,4-DiMBSO ₃ Na	B	168	—	3.0	—	—	—	97	—	≤0.6
2,6-DiMBSO ₃ Na	B	168	—	3.0	—	—	—	97	—	≤0.6
2,4,6-TrMBSO ₃ K	B	0	3.0	1.9	—	1.3	97	14	1.5	1700
		0.9	—	—	—	—	81	14	2.3	
		1.9	0.9	0.2	2.1	0.4	80	13	2.7	
		3.0	0.5	0.1	2.3	0.4	81	—	3.4	
		22.7	—	—	—	3.4	—	93	—	
2,4,6-TrMBSO ₃ H · 2H ₂ O ^h	A	0	25	—	—	—	75	—	—	60
		18.7	18	<0.4	7	—	68	<2	7	
		115	2.4	—	23 ⁱ	—	48	<2	26 ^j	
2,3,4,5-TeMBSO ₃ K	B	168	—	3.0	—	—	—	97	—	≤0.6
2,3,4,6-TeMBSO ₃ K	B	0	3.0	0.6	—	—	97	14	2.0	6200
		0.6	—	—	—	0.3	81	13	2.5	
		1.7	—	0.1	1.9	0.4	82	13	2.7	
		2.6	—	—	2.1	0.5	81	—	—	
2,3,5,6-TeMBSO ₃ K	B	0	3.0	—	—	—	97	12	1.8	1600
		1.2	1.3	0.3	1.2	0.4	83	12	2.5	
		2.2	0.8	0.2	2.0	0.4	82	12	2.8	
		3.4	0.5	0.1	2.3	0.5	81	12	3.6	
		23	—	—	2.6	0.9	—	93	—	
"	C	0	7.0	3.6	—	3.2	93	90	2.7	600
		2.9	1.8	0.6	4.0	0.8	—	89	4.1	
		5.3	1.1	0.2	4.6	0.9	—	88	5.1	
		7.7	—	—	5.2	1.5	—	86	6.7	
		26	—	—	—	—	—	—	—	
PeMBSO ₃ K	B	0	3.0	—	—	—	97	14	3.2	> 30000
		0.3	—	—	2.7	—	79.5	13	3.3	
		1.4	—	—	2.6	—	80	—	—	

^a The amount of PoMBS is 0.08–0.10 mmol, unless stated otherwise. ^b See Experimental. ^c The moment of addition of $\text{CF}_3\text{SO}_3\text{H}$ was taken to be the zero time for all reactions. ^d S stands for SO_3H . ^e Ring protonated species. ^f The anisole was in part protonated on oxygen. ^g Predominantly *p*-anisolesulfonic acid. ^{h,k} The amounts of 2,4,6-TrMBS and 2,3,5,6-TeMBS are 1.0 and 0.2 mmol, respectively. ⁱ A small fraction of the 1,3,5-TrMB was present as supernatant. ^j The *o*-S/*p*-S ratio is 0.13.

rate coefficients are listed in Table I. No transfer sulfonation is observed with 2,4-DiMBS, 2,6-DiMBS and 2,3,4,5-TeMBS. The rate coefficients of the other PoMBS's under the standard reaction conditions (*i.e.* method B, using 0.08–0.10 mmol of PoMBS) increase in the order 2,3,5,6-TeMBS \approx 2,4,6-TrMBS < 2,3,4,6-TeMBS < PeMBS. For 2,3,5,6-TeMBS, the rate coefficient is 2.5 times smaller on using 0.20 instead of 0.09 mmol of the potassium sulfonate reagent and for 2,4,6-TrMBS it is almost 30 times smaller on using 1.0 mmol of the sulfonic acid dihydrate rather than 0.09 mmol of the potassium sulfonate reagent. These reductions are ascribed to the relatively lower acidity of the reaction system as a result of the enhanced concentration of the transfer sulfonation reagent and, in the latter case, also as a result of the additional presence of the water of crystallization²¹.

A simple comparison of the reactivities of 2,4-DiMBS, 2,6-DiMBS, 2,4,6-TrMBS and 2,3,4,5-TeMBS shows that the presence of two methyls *ortho* to the sulfo group and the electronically activating *para*-methyl are prerequisites for the transfer sulfonation to occur. The reactivity of 2,3,5,6-TeMBS (lacking the 4-methyl!) is about equal to that of 2,4,6-TrMBS. Apparently, with the former substrate, the absence of the activating 4-methyl is compensated for by the buttressing effects of the additional 3- and 5-methyl, rendering the relief of steric strain upon forming the σ -complex significantly larger for 2,3,5,6-TeMBS than for 2,4,6-TrMBS. Introduction of a methyl group into 2,4,6-TrMBS and 2,3,4,6-TeMBS leads to a rate increase with a factor of 4 and ≥ 5 , respectively, as a result of the enhanced overcrowding in the reagents. The mechanism for the transfer sulfonation by 2,4,6-TrMBS, as typical reagent,



Scheme 1. Mechanism for transfer sulfonation of anisole by 2,4,6-TrMBS.

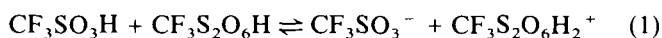
Table II ¹H NMR data of the components of the reaction mixtures.

Compound ^a	Solvent ^a	δ (ppm)					
		1	2	3	4	5	6
2,4,6-TrMBS	CF ₃ SO ₃ H		2.33	6.79	2.04	6.79	2.33
	² H ₂ O ^b		2.57	7.03	2.27	7.03	2.57
	A		2.10	6.24	1.67	6.24	2.10
	B		2.09		1.68		
2,4,6-TrMB + HS	B		2.20		1.82		
2,4,6-TrMB	A	6.30	1.72	6.30	1.72	6.30	1.72
	B	6.28	1.73	6.28	1.73	6.28	1.73
2,4,6-TrMB + H	B		1.82		1.82		1.82
2,3,4,6-TeMBS	B		2.04	1.49	1.64		2.08
2,3,4,6-TeMB	B		1.69	1.55	1.69		1.72
2,3,4,6-TeMB + H	B		1.78	1.64	1.78		1.81
2,3,5,6-TeMBS	B		1.99	1.64		1.64	1.99
2,3,5,6-TeMB + HS	B		2.09	1.99		1.99	2.09
2,3,5,6-TeMB	B	6.30	1.64	1.64	6.30	1.64	1.64
2,3,5,6-TeMB + H	B		1.74	1.74		1.74	1.74
PeMB	B	\sim 6.3	1.70	1.61	1.63	1.61	1.70
PeMB + H	B		1.79	1.66	1.72	1.66	1.79
PhO + HMe ^c \rightleftharpoons PhOMe	B	3.22	6.42	6.76	6.46	6.76	6.42
Ph + HOMe ^d \rightleftharpoons PhOMe	B	3.30	6.5–7.0				
Ph + HOMe ^d	CF ₃ SO ₃ H	3.90	7.22 (4H)				
MeOC ₆ H ₄ -4-S	B	3.15	\sim 6.4	7.30		7.30	\sim 6.4
	² H ₂ O ^b	3.88	7.08	7.76		7.76	7.08
MeOC ₆ H ₄ -2-S	² H ₂ O ^b	3.93		7.79	7.05	7.58	7.19
	CF ₃ SO ₃ H		7.09 (4H)				

^a S stands for SO₃H with the solvent CF₃SO₃H and the reaction mixture systems applying method A and B, whereas S stands for SO₃ with ²H₂O as solvent. ^b pH \approx 7. ^c O-protonated species. ^d C-protonated species.

is shown in Scheme 1. Protonation of the sulfo-group-carrying carbon leads – with release of steric strain – to the indicated σ -complex **1**. This intermediate is proposed to be the actual reagent which sulfonates anisole by transfer of SO_3H^+ to yield the 4- with some 2-anisolesulfonic acid. Evidence in favour of **1** acting as the transfer-sulfonating intermediate comes from our observations that the relatively stable 4,6,8-trimethyl-1-azulenium- and 1,4-dimethyl-7-isopropyl-1-azulenium-1,3-disulfonate σ -complexes are capable of sulfonating 1,3-dimethoxybenzene²³. Interestingly, for the transfer sulfonylation of anisole by methyl 2,4,6-trimethylphenyl sulfone using triflic acid* as catalyst, a somewhat different mechanism – similar to that advanced for transfer benzoylation¹⁷ – was proposed, in which the essential step involves nucleophilic attack of the C(4) of anisole on the sulfur atom of the oxygen protonated sulfone¹⁸. Formally, such a type of mechanism cannot be excluded for the transfer sulfonation. In view of the reversibility of aromatic sulfonation (of, for example, polymethyl-methylbenzenes^{15,24} and 4,6,8-trimethyl- and 1,4-dimethyl-7-isopropylazulene²³), the mechanism shown in Scheme 1 is preferred for the transfer sulfonation.

It is unlikely that $\text{CF}_3\text{SO}_3\text{H}$ acts as a vehicle for the transfer of SO_3H^+ from the 2,4,6-trimethylbenzenonium-1-sulfonic acid ion (**1**) to anisole in view of the observation that the sulfonation of anisole (3.0 mmol), with a matured²⁵ mixture of $\text{CF}_3\text{SO}_3\text{H}$ (2.0 mmol) and SO_3 (1.0 mmol), containing mainly $\text{CF}_3\text{S}_2\text{O}_6\text{H}$ and thus – because of the ionization (**1**)²⁶ – a small amount of the presumed SO_3H^+ transferring entity $\text{CF}_3\text{S}_2\text{O}_6\text{H}_2^+$, was found to lead to a different *ortho/para* substitution ratio (0.35 ± 0.05) than that observed in the transfer sulfonation (0.13 , see Table I, note j)²⁷.



Experimental

Trifluoromethanesulfonic acid, 2,4,6-trimethylbenzenesulfonic acid dihydrate and anisole were high-quality compounds obtained from Janssen Chimica; they were used without further purification. The preparations of the various sodium and potassium polymethylbenzenesulfonates have been described^{15,28}.

Reaction procedures and analysis

Method A. 2.0 mmol of $\text{CF}_3\text{SO}_3\text{H}$ was added at 25°C to a mixture of 3.0 mmol of anisole and 1.0 mmol of 2,4,6-trimethylbenzenesulfonic acid dihydrate to give a homogeneous solution.

Method B. 2.0 mmol of $\text{CF}_3\text{SO}_3\text{H}$ was added at 25°C to a mixture of 3.0 mmol of anisole and 0.20 mmol of the appropriate alkali polymethylbenzenesulfonate. The resulting heterogeneous mixture was vigorously stirred for 2 min and then filtered over glass wool under nitrogen leaving, in the resulting homogeneous solution, 0.08–0.10 mmol of sulfonate.

Method C. The procedure is similar to B and was applied with potassium 2,3,4,5-tetramethylbenzenesulfonate. The vigorous stirring was continued for 40 min, after which time the reaction mixture had become homogeneous.

The progress of the reaction was determined by recording ¹H NMR spectra after appropriate time intervals using a Varian HA-100 spectrometer. The product assignment of the components of the reaction mixtures is given in Table II. The qualitative analyses of the various homogeneous reaction mixtures were performed by applying ¹H NMR multicomponent analysis based on the specific hydrogen absorptions of the various components²⁹. The reaction mixture containing 2,4,6-TrMBS, studied by method A, was eventually quenched with water and neutralized with dilute aqueous potassium hydroxide. After extraction of the aqueous solution with CH_2Cl_2 , the water was removed by freeze-

drying. The remaining potassium sulfonate mixture was dissolved in ²H₂O and a ¹H NMR spectrum recorded.

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- ⁷ The reactive sulfonating entity for sulfuric acid <88% H_2SO_4 is H_3SO_4^+ (i.e. $\text{H}_2\text{O} \cdot \text{SO}_3\text{H}^+$), for 85–100% H_2SO_4 it is $\text{H}_2\text{S}_2\text{O}_7$ ($\text{HSO}_4^- \cdot \text{SO}_3\text{H}^+$), for 100–104% H_2SO_4 $\text{H}_3\text{S}_2\text{O}_7^+$ ($\text{H}_2\text{SO}_4 \cdot \text{SO}_3\text{H}^+$), for >103% H_2SO_4 $\text{H}_2\text{S}_4\text{O}_{13}$ ($\text{HS}_3\text{O}_{10}^- \cdot \text{SO}_3\text{H}^+$ or $\text{HS}_2\text{O}_7^- \cdot \text{S}_2\text{O}_6\text{H}^+$)³, for chlorosulfuric acid it is very likely $\text{ClS}_2\text{O}_6\text{H}$ ($\text{ClSO}_3^- \cdot \text{SO}_3\text{H}^+$)⁴, for methanesulphonic acid it is $\text{MeS}_2\text{O}_6\text{H}$ ($\text{MeSO}_3^- \cdot \text{SO}_3\text{H}^+$)⁵ and for acetylsulfuric acid it is probably $\text{AcOSO}_3\text{H}_2^+$ ($\text{AcOH} \cdot \text{SO}_3\text{H}^+$).
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- ²¹ The acidity is much lower for the polymethylbenzenesulfonic acids than for trifluoromethanesulfonic acid²². This is also apparent from our experiments (cf. Table I), since the $[\text{2,4,6-TrMB}^+\text{H}]/[\text{2,4,6-TrMB}]$ and $[\text{Ph}^+\text{HOME}]/[\text{PhOME}]$ ratios are smaller on using 1.0 mmol of 2,4,6-trimethylbenzenesulfonic acid dihydrate (viz. ≤ 0.10 and ≤ 0.04 , respectively) rather than 0.09 mmol of the corresponding non-hydrated potassium sulfonate (viz. 0.18 and 0.17, respectively).
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