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The sulfonation of aromatic and heteroaromatic polycyclic compounds

Alan R. Katritzky [a,*], Myong Sang Kim [a], Dmytro Fedoseyenko [a], Khalid Widyan [b], Mike Siskin [c], Manuel Francisco [c]

[a] Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, FL 32611-7200, USA
[b] Department of Chemistry, Tafila Technical University, PO Box 179, Tafila, Jordan
[c] ExxonMobil Research and Engineering Company, Corporate Strategic Research Laboratories, 1545 Route 22 East, Clinton Township, Annandale, NJ 08801, USA

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ABSTRACT

Relative reactivities of a series of polycyclic carbo- and heteroaromatic compounds to sulfonation by sulfur trioxide in nitrobenzene are measured and discussed. The results show the following reactivity in decreasing order: indole, carbazole, pyrene, perylene, naphthalene, phenanthrene, benzene, benzothiophene, and dibenzothiophene.

1. Introduction

Electrophilic aromatic substitution reactions such as halogenation,[1] nitration,[2] sulfonation,[3] Friedel–Crafts acylation, and alkylation[4] are of great preparative importance in the production of intermediates vital for the synthesis of many valuable industrial, pharmaceutical, and agrochemicals.

Most electrophilic aromatic substitutions proceed by the arenium ion mechanism (Scheme 1)[5] in which the electrophile attacks the substrate giving rise in the first step a positively charged intermediate (the arenium ion). The leaving group departs in the second step.

In the arenium ion mechanism, the electrophile attacks the ring to give a carbocation, which exists as a resonance hybrid, (**1**), and is frequently represented as in **2**. Ions of this type are called *Wheland intermediates*, *σ complexes*, or *arenium ions*. The arenium ion is generally a reactive intermediate, which undergoes further reaction by loss of either X^+ or Y^+. The second step is to nearly always faster than the first step, so the first step is rate-determining and the overall reaction is second order. A rare mechanism, called the S_E1,[5] occurs when the leaving group departs in the rate-limiting step before the electrophile attacks.

1.1. Previous work on sulfonation

The mechanism of sulfonation can be complex, as it is reversible in many cases, and the reaction rate depends significantly on (1) the nature of the electrophilic species, which may be derived from sulfuric acid or sulfur trioxide; and (2) the reactivity of the aromatic system under attack.[6,7] At low temperature, the reverse desulfonation reaction is very slow and the forward reaction is essentially irreversible. In 85% sulfuric acid the rate-determining step is the addition of the electrophile, thought to be $H_3SO_4^+$ to the aromatic ring; but in stronger acid and oleum the electrophile is believed to be $H_2S_2O_7$ and the loss of the ring proton becomes the rate-determining step (Scheme 2).[8,9]

Sulfonations of aromatic compounds by concentrated or fuming sulfuric acid[3] or pure sulfur trioxide or its pyridine complex[9] are of high industrial importance due to the availability and low cost of the reagents. However, sulfuric acid has some disadvantages: high reaction temperature, long reaction time, formation of waste acid due to the production of water, and environmental pollution. The use of sulfur trioxide (SO_3) as the sulfonating agent is efficient since the direct addition of the SO_3 does not generate water. Other advantages of SO_3 include fast rates, absence of waste acid disposal, and minimal environmental impact.[10]

The kinetics and mechanism of the sulfonation of aromatic compounds using sulfur trioxide has been well studied[11–13] and has been shown to be quite complex. Some review is needed to show that our competition approach removes many of the complexities and quickly and easily provides new relative reactivity data. Sulfo nation of toluene with sulfur trioxide is proposed to proceed initially via the formation of a toluene–S_2O_6 π-complex, which rearranges to form a *Wheland* pyrosulfonate intermediate, which in turn undergoes a facile prototropic rearrangement involving the transfer of the ring hydrogen at the sp^3 carbon to the sulfonate oxygen atom to form toluenepyrosulfonic acid. Once formed, this acid is thought to attack toluene to form 2 equiv of toluenesulfonic acid, which preferentially react with sulfur trioxide to reform the pyrosulfonic acid. When SO_3 dissolved in an aprotic solvent is the reagent, SO_3 is the actual electrophile. Free SO_3 is the most reactive of all sulfonating species, so attack here is generally fast and the subsequent step is usually rate-determining.[9,11]

* Corresponding author. Tel.: +1 352 392 0554; fax: +1 352 392 9119.
E-mail address: katritzky@chem.ufl.edu (A.R. Katritzky).

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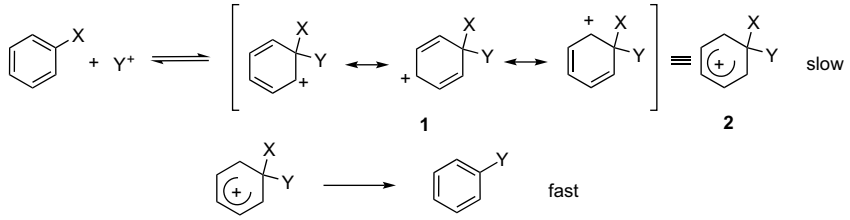
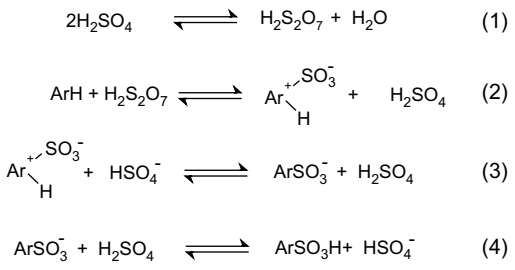


Scheme 1. Arenium ion mechanism of electrophilic aromatic substitution.



Scheme 2. Proposed mechanism of sulfonation on aromatic compounds in H_2SO_4.

The kinetics of aromatic sulfonation have been investigated for a century.[14]

$$-\mathrm{d[Ar]}/\mathrm{d}t = k[\mathrm{Ar}]A^2_{\mathrm{H_2SO_4}}/A_{\mathrm{w}} \quad (1)$$

Eq. 1 has commonly been used to express the aromatic sulfonation rate in aqueous sulfuric acid[15] where [Ar] is the concentration of the aromatic ring to be sulfonated, $A_{H_2SO_4}$ is the reactivity of sulfuric acid, proportional to the concentration of H_2SO_4, A_w is the activity of water, proportional to the concentration of water present, k is the rate constant, and t is the reaction time. The rate is first-order with respect to the aromatic substrate. The second order of the activity of the acid has been rationalized by a reaction of two H_2SO_4 molecules producing the sulfonation species.[16] The presence of water changes the reaction species from SO_3 to $H_3SO_4^+$ and retards the rate and therefore appears as an inverse term. Water as a byproduct slows aromatic sulfonation[17] since it dilutes the sulfuric acid and reduces the reactivity of the sulfonating species.[9] The relationship between the rate and the acid concentration has been studied and summarized.[15] Generally, the experimental conditions necessitate a very low concentration of the aromatic substrate and/or low conversion to reduce the effect of the water byproduct. Some reports show that the rate is clearly first order with respect to the substrate.[18] Other data did not follow the simple first-order term with respect to the substrate. Here the rate gradually decreases from that of the expected first-order rate. However, it is not possible to attribute the retardation simply to water. Aromatic sulfonation by sulfuric acid has been known to be complicated by temperature dependence, isomerization,[19–21] reversibility,[18] further sulfonation[20,21] as well as by the water produced. For example, the sulfonation of naphthalene using 98.5% H_2SO_4 at 25 °C affords naphthalene-1-sulfonic acid, which undergoes further sulfonation leading to 1,5-, 1,6-, and 1,7-naphthalenedisulfonic acids,[20] while sulfonation of naphthalene-2-sulfonic acid with 99.5% H_2SO_4 at 56–57 °C for 5 h gives mixtures of 1,6-, 1,7-, 2,7-, 2,6-disulfonic acids and mixtures of trisulfonic acids (Scheme 3).[21]

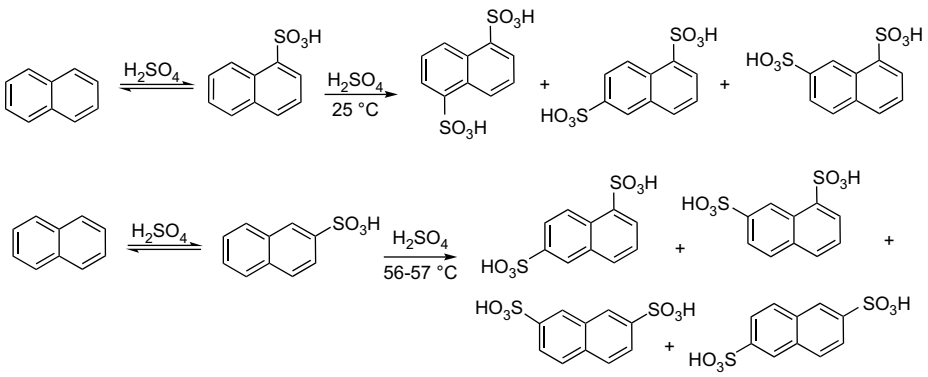
1.2. Objective of the present work

We determined the relative reactivities of a series of polycyclic carbo- and heteroaromatic compounds: benzene, naphthalene, phenanthrene, pyrene, perylene, benzothiophene, dibenzothiophene, carbazole, and indole (Fig. 1) to sulfonation by sulfur trioxide in nitrobenzene, conditions, which have the advantage of relating to a significant amount of published kinetic information.[22–25]

2. Results and discussion

2.1. Preparation of mono sulfonic acids

Standard samples of naphthalene-2-sulfonic acid (**3a**), phenanthrene-2-sulfonic acid (**3b**), 1-pyrenesulfonic acid (**3c**), dibenzothiophene-2-sulfonic (**3d**), indole-3-sulfonic acid (**3e**), perylene-3-sulfonic acid (**3f**), and carbazole-3-sulfonic acid (**3g**) were prepared starting from the corresponding unsubstituted aromatic compounds with sulfur trioxide in nitrobenzene. All compounds had properties in agreement with the literature data (see Section 4).[21,34–39] Benzothiophene sulfonic acid was first reported by Weissgerber.[40] Pailer and Romberger[35] showed the product (88%



Scheme 3. The sulfonation of naphthalene with H_2SO_4.

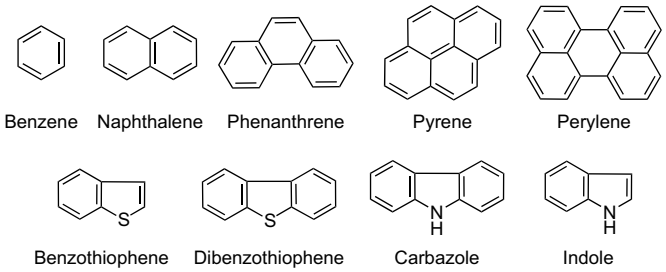


Figure 1.

yield) was either the 2- or 3-isomer by IR; in 1967, American authors identified it as 3-isomer from long range NMR coupling.[41]

2.2. Relative reactivity by internal competition

Relative reactivities were obtained by a direct competition between equimolar amounts of two aromatic compounds, **A** and **B**, well mixed in nitrobenzene at 0–40 °C prior to the addition of 0.5 equiv of SO_3. Although the reaction was rapid, analyses were not made until 4 h after mixing for convenience. They were run on a much larger scale than required for the analysis so as to allow a more accurate measure of the ratios of unreacted starting substrates and substitution products to be obtained. The filtered mixture was analyzed for the reactants using a gas chromatograph–mass spectrometer (Hewlett-Packard Model 5972 Series). The results are summarized in Table 1 in terms of (i) the ratio of unreacted compound **A** to unreacted compound **B** in the filtrate and (ii) the relative reactivity order of compounds compared to dibenzothiophene considered as 1.[26]

To determine the relative reactivity of indole and carbazole, the mixed sulfonic acids were converted into volatile silyl derivatives for analysis by GC–MS. Sulfur trioxide (0.05 mL, 1 mmol) was added to a stirred solution of indole (1 mmol) and carbazole (20 mmol) in nitrobenzene (20 mL) and the mixture was stirred at room temperature for 4 h. The solid was filtered and dried: ^{1}H NMR showed a variety of aromatic signals. Analysis of the filtrate directly by GC–MS showed only carbazole.

The ^{t}BDMS derivatives of the sulfonic acids were prepared by adding ^{t}BDMSCl and MTBSTF to mixture of sulfonic acids. The reaction mixture was stirred at 70 °C for 40 h and analyzed by GC–MS. A gas chromatograph–mass spectrometer (Hewlett–Packard Model 5972 Series) was used. Each R-SO_3-Si$Me_2{}^t$Bu displayed fragment ions m/z characteristic of R-SO_3-Si$Me_2{}^t$Bu function and $[M-SO_3(^tBDMS)]^+$ corresponding to loss of amu 195 from the molecular ion.[27–29]

The reactivity order of the model compounds toward sulfonation using SO_3-nitrobenzene can then be arranged as shown below, which shows the high reactivity of heterocyclic compounds containing a pyrrolic-nitrogen atom and of the larger aromatic ring systems (Table 2).

The results obtained for the sulfonation reaction in Table 1 shows that the reactivity orders of pyrene to phenanthrene and naphthalene to benzene are 30 to 1 and 6.9 to 1, respectively, in agreement with the mononitration results obtained by Dewar and Pryor.[30,31] The reactivity order toward mononitration is 29 to 1 for pyrene to phenanthrene and 6 to 1 for naphthalene to benzene.

Our results also show the reactivity of naphthalene to phenanthrene is 3 to 1, which is in agreement with the results obtained by Gore et al. by a competitive reactivity study on Friedel–Crafts acyl ation of phenanthrene with naphthalene (2.8 to 1).[32] Finally, our competitive sulfonation reaction of phenanthrene and benzene with sulfur trioxide shows the reactivity of phenanthrene to benzene is 2.3 to 1, which agrees with the results obtained by Pryor et al. for mononitration of phenanthrene and benzene (2.6 to 1).[31] Because the reactivity of indole is so much greater than that of carbazole the concentration ratio of the unreacted materials has a high degree of uncertainty and this is reflected in the approximate reactivity ratio.

3. Summary

The relative reactivities of our polycyclic carbo- and heteroaromatic compounds to electrophilic sulfonation with sulfur trioxide in nitrobenzene are quite similar to those in the literature for electrophilic nitration and acetylation.

4. Experimental section

4.1. General

Melting points were determined on a hot-stage apparatus and are uncorrected. NMR spectra were recorded using DMSO-d_6 using TMS for ^{1}H (300 MHz) and ^{13}C (75 MHz) as the internal standard.

Table 1

Entry	Compound **A**	Compound **B**	Concn ratio[a]	Relative ratio	Relative reactivity[b]
1	*Indole*	Carbazole	1.0:96	1.0×10^{-4}:3.0×10^{-3}	~9000:3.3×10^{2}
2	*Carbazole*	Pyrene	1.0:2.8	3.0×10^{-3}:9.0×10^{-3}	3.3×10^{2}:1.1×10^{2}
3	*Pyrene*	Perylene	1.0: 2.2	4.1×10^{-3}:9.0×10^{-3}	1.1×10^{2}:5.0×10^{1}
4	*Pyrene*	Naphthalene	1.0:10	9.0×10^{-3}:9.0×10^{-2}	1.1×10^{2}:1.1×10^{1}
5	*Naphthalene*	Phenanthrene	1.0:3.0	9.0×10^{-2}:2.8×10^{-1}	1.1×10^{1}:3.6
6	*Phenanthrene*	Benzene	1.0:1.6	6.3×10^{-1}:1.0	1.6:1.0
7	*Phenanthrene*	Benzothiophene	1.0:2.2	2.8×10^{-1}:6.3×10^{-1}	3.6:1.6
8	*Benzene*	Benzothiophene	1.0:1.0	6.3×10^{-1}:6.3×10^{-1}	1.6:1.6
9	*Benzothiophene*	Dibenzothiophene	1.0:1.6	6.3×10^{-1}:1.0	1.6:1.0

More reactive compounds are italicized.

[a] Concn ratio of unreacted compound **A**:unreacted compound **B** based on GC–MS analysis of the filtrate.

[b] Relative reactivity order of compounds compared to dibenzothiophene considered as 1 and calculated from 1/[relative ratio].[26]

Table 2

System	Indole	Carbazole	Pyrene	Perylene	Naphthalene	Phenanthrene	Benzene	Benzothiophene	Dibenzothiophene
Order	~9000	330	110	50	11	3.6	1.6	1.6	1.0

4.2. General procedure for preparation of sulfonic acids 3a–f

Model compound (5 mmol) in nitrobenzene (5 mL) was placed in a three-neck round bottom flask equipped with thermometer and drying tube and cooled in an ice bath. Sulfur trioxide (0.23 mL, 5 mmol) was added dropwise using a syringe (the temperature rose to 40 °C upon addition SO_3), the ice bath was removed, and the mixture was stirred at room temperature for 4 h. The solid was collected by filtration, washed with nitrobenzene and dried to give the corresponding sulfonic acid. *Warning*: Due to hazardous properties of sulfur trioxide, all work should be performed in a well-ventilated chemical fume-hood. Personnel handling this material should use adequate protective clothing and rubber gloves.

4.2.1. Naphthalene-2-sulfonic acid (**3a**)[21]

Yield 62%; white microcrystals; mp 97–100 °C (lit. mp 102 °C); ^{1}H NMR (DMSO-d_6): 7.93–7.97 (m, 2H), 8.13–8.16 (m, 1H), 8.29–8.45 (m, 3H), 8.59–8.62 (m, 1H); ^{13}C NMR (DMSO-d_6): 123.9, 124.4, 126.7, 126.9, 127.7, 127.8, 128.7, 132.3, 133.0, 145.0.

4.2.2. Phenanthrene-2-sulfonic acid (**3b**)[33]

Yield 81%; white microcrystals; mp 149–151 °C (lit. mp 150 °C); ^{1}H NMR (DMSO-d_6): 8.06–8.11 (m, 1H), 8.14–8.23 (m, 4H), 8.29–8.32 (m, 2H), 8.50–8.53 (m, 1H), 9.15–9.18 (m, 1H); ^{13}C NMR (DMSO-d_6): 123.8, 123.9, 124.3, 124.9, 124.5, 126.4, 126.8, 127.0, 127.4, 127.9, 130.2, 130.7, 141.7.

4.2.3. Pyrene-1-sulfonic acid (**3c**)[34]

Yield 82%; light green microcrystals; mp 115–118 °C (lit. mp 118–119 °C); ^{1}H NMR (DMSO-d_6): 8.06–8.11 (m, 1H), 8.14–8.23 (m, 4H), 8.29–8.32 (m, 2H), 8.50–8.53 (m, 1H), 9.15–9.18 (m, 1H); ^{13}C NMR (DMSO-d_6): 124.0, 124.4, 125.0, 125.6, 126.5, 126.9, 127.0, 127.5, 127.9, 130.3, 130.9, 131.5, 141.8.

4.2.4. Dibenzothiophene-2-sulfonic acid (**3d**)[36]

Yield 78%; white microcrystals; mp 126–129 °C (lit. mp: unreported); ^{1}H NMR (DMSO-d_6): 7.49–7.56 (m, 2H), 7.76–7.80 (m, 1H), 7.98–8.06 (m, 2H), 8.34–8.40 (m, 1H), 8.51–8.53 (m, 1H); ^{13}C NMR (DMSO-d_6): 118.9, 122.2, 122.5, 123.3, 124.9, 125.1, 127.4, 134.4, 135.1, 138.9, 139.1, 145.3.

4.2.5. Indole-3-sulfonic acid (**3e**)[37]

Yield 85%; white microcrystals; mp 312 °C (lit.[37a] mp: 315 °C); ^{1}H NMR (DMSO-d_6): 7.25–7.36 (m, 1H), 7.44–7.48 (m, 3H), 7.76–7.80 (m, 1H), 7.99–8.15 (m, 1H); ^{13}C NMR (DMSO-d_6): 110.5, 112.2, 121.7, 123.2, 124.5, 126.9, 130.8, 139.7.

4.2.6. Carbazole-3-sulfonic acid (**3f**)[38]

Yield 71%; white microcrystals; mp 160–163 °C (lit. mp: unreported); ^{1}H NMR (DMSO-d_6): 7.12–7.18 (m, 1H), 7.36–7.48 (m, 2H), 7.55–7.72 (m, 2H), 8.05–8.15 (m, 1H), 8.30–8.36 (m, 1H); ^{13}C NMR (DMSO-d_6): 119.3, 122.4, 122.9, 123.7, 124.7, 125.4, 128.0, 134.5, 134.9, 138.8, 140.1, 144.9.

4.3. General procedure for the competition kinetics

Sulfur trioxide (0.23 mL, 5 mmol) was added to a mixture of **A** (5 mmol) and **B** (5 mmol) (Table 1) in nitrobenzene (5 mL) under ice cooling. The mixture was stirred at room temperature for 4 h, filtered, and washed with nitrobenzene (2 mL). The filtrate was analyzed using a gas chromatograph–mass spectrometer (Hewlett–Packard Model 5972 Series). Filtrate, 1 μL, was injected at an oven temperature of 100 °C and after 3 min the temperature was programmed to increase 10 °C/min until 250 °C. The GC–MS analysis is summarized in Table 1.

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