J. Org. Chem. **1993,** *58,* 2605-2613

Photochemistry of Dimethoxybenzenes in Aqueous Sulfuric Acid[1]

Renée Pollard, Susan Wu, Guangzhong Zhang, and Peter Wan*

Department of Chemistry, Box 3055, University of Victoria, Victoria, British Columbia, Canada V8W 3P6

Received January 22, 1993

The photochemistry of the three isomeric dimethoxybenzenes (**1**–**3**) has been studied in aqueous sulfuric acid. Two processes were found to take place: (i) photoprotonation of the ring resulting in exchange of the ring protons, which was observed for all three compounds and (ii) ipso substitution of the methoxy group by water, which was observed only for 1,2-dimethoxybenzene (**3**). Both of these photochemical reactions were catalyzed by acid, requiring acidities stronger than pH(D) 2 for observable reaction. Quantum yields for proton exchange and ipso substitution are reported as a function of medium acidity. The fluorescence emissions of all three compounds were quenched by acid, to give sigmoid type quenching curves, that have a complementary relationship with the corresponding plots of quantum yield of exchange vs acidity, consistent with protonation of the benzene ring in S_1 as the primary photochemical step, to give cyclohexadienyl cation intermediates. Stern–Volmer analysis of fluorescence quenching by proton gave photoprotonation rates in the range $0.09–2.2 \times 10^9$ M^{-1} s^{-1}. The results of this work demonstrate unambiguously that methoxy-substituted benzenes are much stronger bases in S_1 ($pK_{BH+} \simeq 1$ to -2) than in the ground state. This enhanced basicity is manifested in regioselectivity of exchange of **1** and **3** and ipso substitution chemistry of **3**, processes not observed in the ground states of these compounds.

Introduction

Hydrogen exchange via electrophilic attack of a proton on the aromatic ring is the most elementary of all electrophilic aromatic substitution reactions and therefore is a reaction of fundamental interest.[2] It may also be viewed as an acid–base reaction in which the π system of the aromatic ring serves as the base. In general, the π systems of aromatic compounds are very weak bases: the $pK_{BH}{}^+$ for an activated compound such as 1,3,5-trimethoxybenzene is approximately −6.[3] There is evidence to indicate that many aromatic compounds become vastly more basic in the first excited singlet state (S_1). The phenomenon of fluorescence quenching of aromatic compounds by protons can be associated with either (i) photoprotonation or proton-assisted reaction of the reactive side chain in such compounds as styrene, phenylacetylene, and 2-methoxybenzyl alcohol[4] or (ii) simple photoprotonation of the π system of the aromatic ring for compounds such as anisole, naphthalene, and 1-methoxynaphthalene.[5,6] Stevens and Strickler[6a] studied the excited state H–D exchange of naphthalene in aqueous H_2SO_4. Exchange quantum yields of α-deuterionaphthalene were in the range 0.00019–0.033 over the 30–64% H_2SO_4 used. Fluorescence quenching by H_2SO_4 was interpreted as being due to protonation of S_1. Shizuka and Tobita[6b,c] reported that 1-methoxynaphthalene undergoes observable excited state H–D exchange at much lower acidity ($\Phi = 0.24$ in 4:1 $D_2O–CH_3CN$ with 0.1 M D_3O^+). The exchange was regioselective at the 5-position, as determined by analysis of the product by ^1H NMR. However, 2-methoxynaphthalene was unreactive under similar conditions. Fluorescence quenching by acid was observed only for the reactive compound and the resulting k_q was used to estimate a deuteration rate constant of 1.1×10^8 M^{-1} s^{-1}.

Reports of the deuterium exchange of substituted benzenes have also appeared but unlike the naphthalenes, little quantitative data is available.[5] Using Förster cycle calculations Mason and Smith[5e] estimated that the pK_{BH+} of several simple aromatic compounds (benzene, toluene, and naphthalene) to be in the range +5 to +10, indicating that they become much stronger bases in S_1. However, no isotope (deuterium or tritium) exchange was observed and the authors concluded that prototropic equilibrium is not established during the lifetime of the excited state. Smith[5f] also showed that the fluorescence emissions of anisole and the three isomeric dimethoxybenzenes were all quenched significantly in moderately concentrated H_2SO_4. However, since no hydrogen exchange was observed it was concluded that prototropic equilibrium was not attained and that the fluorescence quenching phenomenon was due to a proton-induced radiationless deactivation process but with no exchange. Recent studies by McClelland et al.[7] have shown that the expected cyclohexadienyl cation intermediates from some of the above photoprotonation reactions can be detected via laser flash photolysis in 1,1,1,3,3,3-hexafluoro-2-propanol (HFP).

---

[1] Some of these results have appeared in preliminary form: Wan, P.; Wu, P. *J. Chem. Soc., Chem. Commun.* **1990**, 822.

[2] Norman, R. O. C.; Taylor, R. *Electrophilic Substitution in Benzenoid Compounds*; Elsevier: New York, 1965; Chapter 8.

[3] (a) Liler, M. *Reaction Mechanism in Sulfuric Acid*; Academic Press: London, 1971. (b) Stewart, R. *The Proton: Applications to Organic Chemistry*; Academic Press: Orlando, 1985.

[4] (a) Wan, P.; Yates, K. *Rev. Chem. Intermed.* **1984**, *5*, 157. (b) Wan, P.; Culshaw, S.; Yates, K. *J. Am. Chem. Soc.* **1982**, *104*, 2509. (c) Wan, P.; Yates, K. *J. Org. Chem.* **1983**, *48*, 869. (d) Rafizadeh, K.; Yates, K. *J. Org. Chem.* **1984**, *49*, 1500. (e) Turro, N. J.; Wan, P. *J. Photochem.* **1985**, *28*, 93. (f) Wan, P.; Chak, B. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1751. (g) Wan, P.; Chak, B.; Krogh, E. *J. Photochem. Photobiol., A* **1989**, *46*, 49.

[5] (a) Cornelisse, J.; Havinga, E. *Chem. Rev.* **1975**, *75*, 353. (b) de Bie, D. A.; Havinga, E. *Tetrahedron* **1965**, *21*, 2395. (c) Lodder, G.; Havinga, E. *Tetrahedron* **1972**, *28*, 5583. (d) Spillane, W. J. *Tetrahedron* **1975**, *31*, 495. (e) Mason, S. F.; Smith, B. E. *J. Chem. Soc. (A)* **1969**, 325. (f) Smith, B. E. *J. Chem. Soc. (A)* **1969**, 2673. (g) Kuzmin, M. G.; Uehinov, B. M.; Gyorgy, G. S.; Berezin, I. V. *Russ. J. Phys. Chem. (Engl. Transl.)* **1967**, *41*, 400. (h) Vesley, G. F. *J. Phys. Chem.* **1971**, *75*, 1775. (i) Colpa, J. P.; Maclean, C.; Mackor, E. L. *Tetrahedron, Suppl.* **1963**, *2*, 65.

[6] (a) Stevens, C. G.; Strickler, S. J. *J. Am. Chem. Soc.* **1973**, *95*, 3922. (b) Shizuka, H.; Tobita, S. *J. Am. Chem. Soc.* **1982**, *104*, 6919. (c) Shizuka, H. *Acc. Chem. Res.* **1985**, *18*, 141.

[7] (a) McClelland, R. A.; Cozens, F.; Steenken, S. *Tetrahedron Lett.* **1990**, 3821. (b) Mathivanan, N.; Cozens, F.; McClelland, R. A.; Steenken, S. *J. Am. Chem. Soc.* **1992**, *114*, 2198. (c) Steenken, S.; McClelland, R. A. *J. Am. Chem. Soc.* **1990**, *112*, 9648.

0022-3263/93/1958-2605$04.00/0

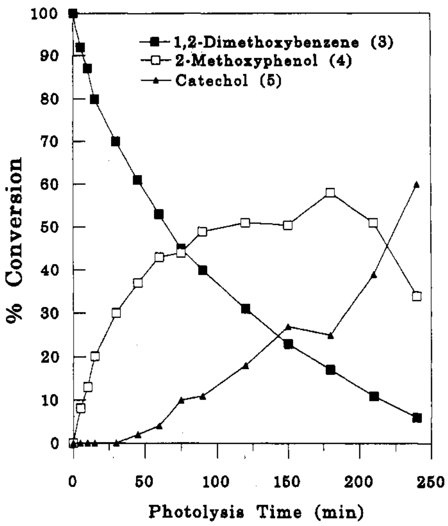
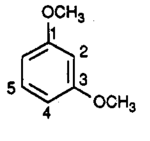
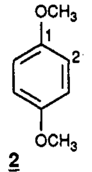


Figure 1. Yields of photoproducts as a function of irradiation time in the photolysis of 1,2-dimethoxybenzene (3) in 2:1 10% H_2SO_4–CH_3CN solution (λ_{excit} = 254 nm).

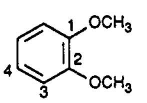
We recently reported that a variety of alkoxy-substituted benzenes undergo facile deuterium exchange on the ring upon photolysis in aqueous D_2SO_4.[1] In addition, 1,2-dialkoxy-substituted benzenes also react via an acid-catalyzed ipso substitution pathway. We now report our full account of the photochemistry of the three isomers of dimethoxybenzene (1–3) in aqueous sulfuric acid. The



1



2

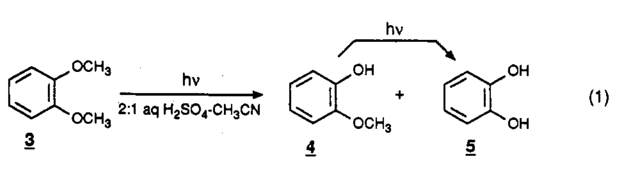


3

results give insight into the synergistic effect of two methoxy groups in controlling photochemical electrophilic substitution mechanisms by proton, which are very different from what is known in the ground state.

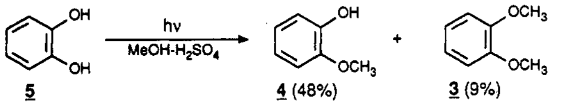
Results and Discussion

Product Studies in Aqueous H_2SO_4. The three isomeric dimethoxybenzenes 1–3 were purchased from Aldrich and used as received after a purity check by GC, which showed they were of >98% purity. Photolysis of 10^{-3} M of 1 and 2 in 2:1 aq H_2SO_4–CH_3CN (pH 7 to 30% H_2SO_4; Rayonet RPR 100 photochemical reactor; 254 nm; 5–30 min) gave no observable reaction as indicated by GC and ^1H NMR, and the substrates could be recovered unchanged. However, photolysis of 3 as above at acidities greater than pH 1 gave 1-hydroxyanisole (4, guaiacol) and catechol (5) (eq 1) with yields that were dependent on



(1)

photolysis time, as determined by GC analysis (Figure 1). The identity of the photoproducts was confirmed by GC/MS and by coinjection with authentic materials. Overall reactivity of 3 was highly dependent on the acidity of the medium with no reaction being observed at pH > 1, even on prolonged photolysis. No reaction was observed in the dark over prolonged times at acidities up to 40% H_2SO_4. The delayed appearance of catechol (5) and the gradual loss of 2-methoxyphenol (4) at photolysis times >100 min (Figure 1) suggests that 5 is a secondary photoproduct from photolysis of 4. This was confirmed by independent photolysis of 4, which gave 5 as the only product. That water is acting as the nucleophile in an ipso substitution process for the methoxy group (as opposed to a demethylation mechanism) was suggested by the results of a photolysis of 5 (60 min) in a solution of 175 mL MeOH containing 25 mL concd H_2SO_4, which gave 4 (48%) and 3 (9%) (eq 2). Again, a plot of yield of photoproducts vs

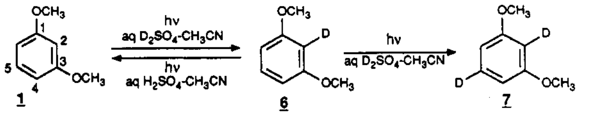


(2)

photolysis time showed that 4 and 5 were the primary and secondary photoproducts, respectively. The ipso substitution process was further confirmed via ^{18}O-labeling experiments (vide infra).

Isotope Labeling Experiments. Photolysis of 3 was carried out in 2:1 30% H_2SO_4–CH_3CN in which the water component of the aqueous H_2SO_4 portion was enriched with 20% ^{18}O, to determine the mechanism of the photosubstitution process. The GC/MS data of the product mixture (60% conversion) showed that 4 was enriched with 20% ^{18}O. The mass spectrum of 5 showed 36% and ~3% enrichments at M + 2 (one ^{18}O) and M + 4 (two ^{18}O), respectively, which is consistent[8] with a secondary ipso substitution process at the remaining methoxy group of 4, as would be expected based on the initial finding of a simple ipso substitution mechanism for the first methoxy group. These results show conclusively that water is the nucleophile in the ipso substitution reaction.

The requirement of acid for the ipso photosubstitution pathway observed only for 3 suggests that photoprotonation of the aromatic ring may be the primary step in the reaction. This opened up the mechanistic possibility that all three isomers (1–3) may react via photoprotonation but with only 3 leading to net photoproduct. Thus the possibility of deuterium exchange on the aromatic ring of these compounds was examined in 2:1 aqueous D_2SO_4–CH_3CN (pD 10–30% D_2SO_4). No observable deuterium incorporation was observed (GC/MS and 250 MHz ^1H NMR) for any substrate in the pD 10–2 range, even on prolonged (>1 h) photolysis. Photolysis of 1 at acidities greater than pD 2 resulted in regioselective exchange of the proton at C2 (H2), as determined by 360 MHz ^1H NMR (eq 3). Proton H2 of unreacted 1 appears as a triplet



(3)

(δ 6.45, J = 3 Hz). After 30-min photolysis in 10% D_2SO_4, the area of this triplet decreases to 40% of the initial value (60% deuterium incorporation), relative to the area of H5, which remained as an unchanged triplet (δ 7.17, J = 8 Hz). Proton H4, which was originally a doublet of doublets (δ 6.51, J = 3 and 8 Hz) now resembles a doublet (J = 8 Hz) with some residual peaks from substrate,

---

[8] The expected enrichments are 32% (M + 2) and 4% (M + 4), based on a simple substitution for the second methoxy group by $H_2{}^{16}O$ and $H_2{}^{18}O$, assuming no secondary isotope effect (from $H_2{}^{18}O$) for reaction.

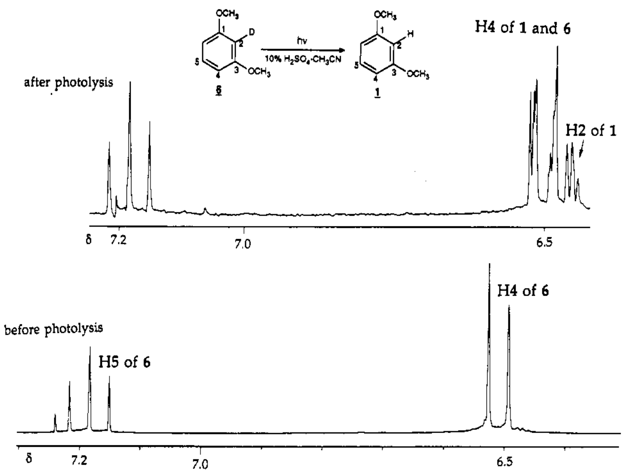


Figure 2. ^{1}H NMR (250 MHz) spectra of the regioselective protonation and exchange of **6** in 10% H_2SO_4. Lower spectrum: **6** before photolysis. Upper spectrum: a mixture of **6** (60%) and **1** (40%) observed after photolysis.

consistent with the replacement of H2 by deuterium since couplings to deuterium are difficult to resolve. Analysis of the same sample by GC/MS indicated a deuterium content of $\simeq$60% confirming the NMR assignment. On extended photolysis (>2 h), complete exchange of H2 by deuterium was possible. In these runs, the protons at C4 appear as a doublet (J = 8 Hz) with a residual singlet at the same position, which can be assigned to dideuterated derivative **7**. The product mixture in these long photolysis runs was also contaminated with some thermal exchange products. For example, the growth of a doublet and a singlet at H5 is consistent with **6** reacting further to incorporate one and a second deuterium at positions 4 and 6 (vide infra). No attempts were made to quantify the proportions of the various possible dideuterated isomers.

The regioselective photoexchange at the 2-position of **1** is best illustrated by studying the photoexchange of 1,3-dimethoxybenzene-2-*d* (**6**) in aqueous H_2SO_4. The ^{1}H NMR (250 MHz) of this compound (made via ortho lithiation of **1** with n-BuLi followed by quenching of the anion with D_2O) (Figure 2) shows the expected doublet for H4 (δ 6.52, J = 8 Hz) and triplet for H5 (δ 7.18, J = 8 Hz). After photolysis (20 min), a new triplet of H2 (δ 6.47, J = 3 Hz) has grown in due to formation of **1** ($\simeq$40% yield by integration). Note also that the set of doublet of doublets due to H4 of **1** is now superimposed onto the doublet at δ 6.52 of **6**. A plot of yield of **1** versus photolysis time is shown in Figure 3 which illustrates that the exchange can be taken to very high conversion. Photolysis of **6** in 2:1 5% D_2SO_4–CH_3CN for 2 h resulted in a ^{1}H NMR spectrum which is similar to that observed on extended photolysis of **1** in aqueous D_2SO_4, consistent with formation of some **7**. Again, the product mixture was contaminated with some products of thermal exchange at the 4- and 6-positions of **6**.

Thermal exchange of **1** was observable at acidities $\geq$10% D_2SO_4. When a sample of **1** was prepared in 2:1 30% H_2SO_4–CH_3CN and left in the dark for 1 h, the resulting ^{1}H NMR was consistent with exclusive exchange of H4, to give **8** and some **9**. Thus, the signals for H2 and H4 remained essentially unchanged (in low conversion runs) whereas the resonance at δ 7.17 of H5 becomes more complicated. It is composed of the original triplet (J = 8 Hz) due to unreacted **1**, a new doublet (J = 8 Hz) due to **8** and a singlet due to **9**. GC/MS analysis of this sample

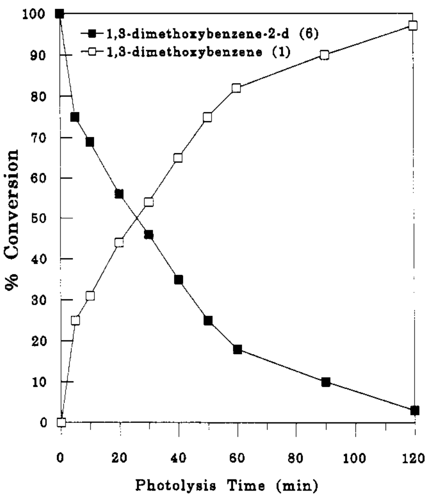
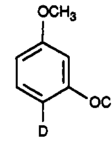
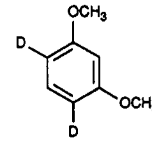


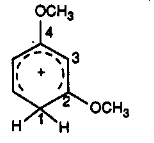
Figure 3. Plot of yield of **1** vs photolysis time on photolysis of **6** in 10% H_2SO_4.



8



9



10

showed both monodeuterated (45%) and dideuterated products (34%), respectively, consistent with the NMR assignment, although it was not possible to calculate % yields using NMR integration since all the peaks at δ 7.17 overlapped significantly. Deuteration of H5 was not observed in any thermal run and supports the notion that the 5-position is photochemically activated, although to a much lesser extent than the 2-position. The regioselective protonation at C4 of ground state **1** shown here is consistent with findings by Kresge and co-workers[9,10] who have measured the rates of detritiation of 1,3-dimethoxybenzene-4-*t* and 1,3-dimethoxybenzene-2-*t*, in which the former reacted 5 times faster and showed that in 95% H_2SO_4 **1** is completely protonated at C4 to give 2,4-dimethoxybenzenoium ion (**10**).

Photochemical incorporation of deuterium was also observable when **2** was irradiated in aqueous D_2SO_4 although the yields were lower than for **1** at the same acidity. However, since **2** does not have any observable dark exchange up to $\simeq$40% H_2SO_4 (due to the deactivating effect of a meta-substituted methoxy group), the photochemical reaction could be studied at much higher acidities than those used for **1**. Photolysis of **2** in 2:1 20% D_2SO_4–CH_3CN for 1 h resulted in $\simeq$20% monodeuterium incorporation by GC/MS. The 250-MHz ^{1}H NMR showed a loss of signal intensity of H2 relative to the methoxy protons with no changes in the splitting patterns (both remained as sharp singlets). Thus it is safe to conclude that the exchange takes place at C2 and not at the methoxy group.

Studying the photochemistry of **3** in aqueous D_2SO_4 provided data regarding the extent of deuterium incorporation in recovered **3** as well as any deuterium incorporation in the primary photoproduct **4**. For the same reason as **2**, **3** was not very reactive towards thermal

---

(9) Kresge, A. J.; Chiang, Y.; Hakka, L. E. *J. Am. Chem. Soc.* 1971, *93*, 6167.

(10) Kresge, A. J.; Mylonakis, S. G.; Sato, Y.; Vitullo, V. P. *J. Am. Chem. Soc.* 1971, *93*, 6181.

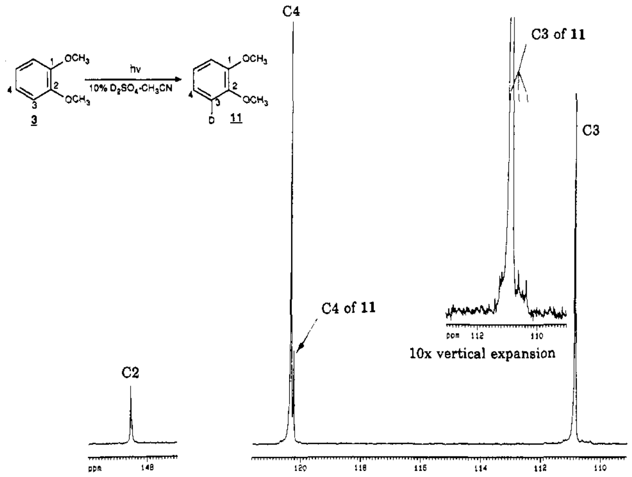


Figure 4. ^{13}C NMR (90.6 MHz) spectra of recovered **3** on photolysis in 10% D_2SO_4.

exchange under the conditions used and the photochemical reaction could be studied at moderately high acidities. Photolysis of **3** (50 mg; 1.5 h) in 2:1 10% D_2SO_4–CH_3CN was repeated seven times (total conversion to **4** and **5** of each photolysis was ≃75%) and the product mixtures combined. Substrate **3** was separated from **4** and **5** by washing the organic extract with 0.1 M NaOH followed by final purification by prep TLC. GC/MS analysis of recovered **3** indicated 30% monodeuterium incorporation. Since protons H3 and H4 of **3** could not be resolved by 360-MHz NMR, we resorted to use of ^{13}C NMR (90.6 MHz) for the determination of location of deuterium. Shown in Figure 4 is the portion of the ^{13}C NMR spectrum of the benzene ring carbons of recovered **3**. The carbon resonance of the methoxy group remained unchanged after photolysis and is therefore not shown. The carbon assignments of the three ring carbons shown were made using standard tables of ^{13}C NMR shifts for substituted benzenes and agrees well with similar compounds tabulated in the literature.[11] Analysis of the spectrum indicates that there is a weak triplet at δ 110.6 (J = 24 Hz) which is slightly upfield from the resonance of C3. In addition, a weak singlet also appears slightly upfield to C4. This data is consistent with formation of **11**. Slight upfield shifts of carbon resonances are well-known upon deuterium incorporation. In addition, the observed 24-Hz coupling in the "1:1:1" triplet is typical for ^{13}C–^{2}H. The C4 resonance of **11** is resolvable while that of C2 was not, perhaps due to the latter peak's much weaker intensity.

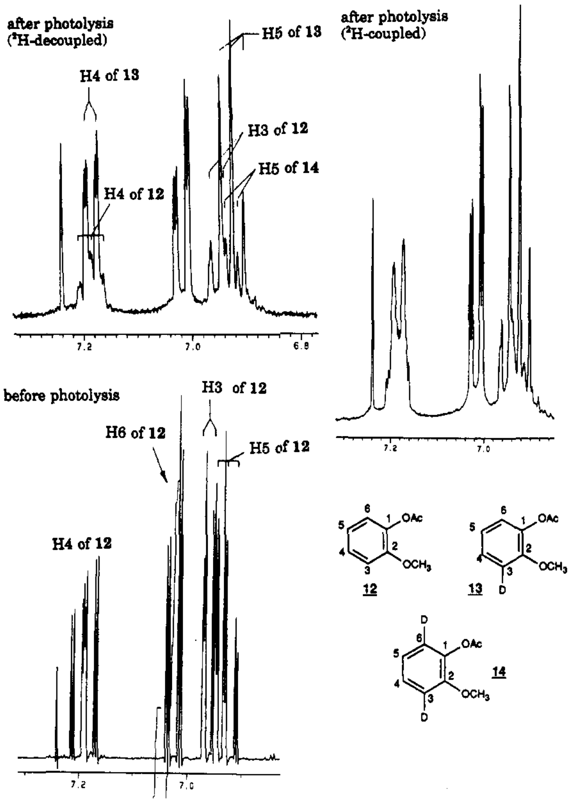
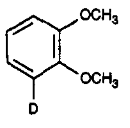
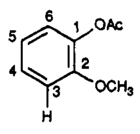


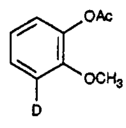
Figure 5. ^{1}H NMR (360 MHz) spectra of deuterium incorporation in ipso photoproduct **4** (as the acetate) on photolysis of **3** in 10% D_2SO_4.



11

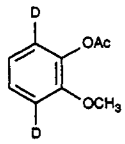


12

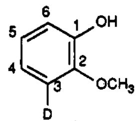


13

For analysis of location of deuterium in photoproduct **4**, lower conversions were employed to avoid formation of **5**. Samples (50 mg) were irradiated for 15 min in 2:1 10% D_2SO_4–CH_3CN. The phenol product **4** (conversion 16%) was separated from **3** by base extraction. Further purification of photoproduct **4** was carried out using prep TLC to ensure there were no traces of **5**. Since the four aromatic protons of **4** were not resolvable by 360 MHz ^{1}H NMR, it was converted to the acetate using Ac_2O, in which the four protons were well-resolved (Figure 5). Shown in the lower portion of Figure 5 is the aromatic portion of the spectrum of undeuterated acetate **12** with the peaks assigned using standard tables of proton resonances of substituted benzenes as well as the observed splitting patterns. Since GC/MS showed that photoproduct **4** is significantly monodeuterated (≃60%) as well as ≃12% dideuterated, significant changes in the spectra of the photoproduct were anticipated. Shown at the top of Figure 5 are the spectra (one of which was deuterium decoupled) of the acetate derivative of the photoproduct. The peak area of the resonance of H3 is substantially reduced, clearly indicating that it is this proton which has exchanged (i.e., formation of **13** as the major product). The areas of the other protons remained essentially unchanged except for changes in multiplicity. For example, H5 of **13** appears as a cleaner "triplet" since coupling to deuterium at C3 of **13** is absent in the ^{2}H-decoupled spectrum. The peak for H4 (^{2}H-decoupled spectrum) is composed of the original doublet of triplets (due to **12**) and a more intense doublet of doublets (due to H4 of product **13**). The second deuterium is most probably located at C6 (product **14**) since there is a residual new doublet at H5. Incorporation of the second deuterium at C4 would also give rise to this doublet at H5 but an additional doublet due to H6 would also be expected, which is not evident in the ^{2}H-decoupled spectrum although a residual amount may have gone undetected with the quality of spectra available. We conclude that



14



15

---

[11] Hayamizu, K., Yamamoto, O., Eds. *^{13}C NMR Spectra of Polycyclic Aromatic Compounds*; Japan Industrial Technology Association: Tokyo, 1982.

Table I. Product Quantum Yields as a Function of Medium Acidity

medium acidity (pD or % D_2SO_4)[b]	Φ[a]				
	1[c]	**6**[d]	**2**[c]	**3**[c]	**4**[e]
7.4	0	0	0	0	0
2.4	0.032	0.040	0.028	0.012	0.000
1.9	0.039	0.048	0.034	0.013	0.000
1.6	0.048	0.058	0.039	0.014	0.000
1.4	0.064	0.063	0.042	0.015	0.000
1.20	0.075	0.072	0.048	0.016	0.002
0.90	0.10	0.078	0.051	0.018	0.003
0.75	0.13	0.086	0.054	0.018	0.010
0.60	0.19	0.090	0.060	0.020	0.015
5%	0.22	0.10	0.068	0.021	0.021
10%	0.29	0.11	0.096	0.027	0.050

[a] Measured using GC/MS or GC for analysis (254-nm lamps from a Rayonet RPR 100 photochemical reactor; merry-go-round apparatus). Estimated error, 15% of quoted value. [b] 20% CH_3CN cosolvent used. Quote pD or D_2SO_4 is of the aqueous portion. For quantum yield entries of **6**, acidity quoted is pH (or % H_2SO_4), and 0.40 should be subtracted from the quoted "pD" to obtain the actual pH value used for this compound. The quoted % (w/w) D_2SO_4 (H_2SO_4) values were calculated from weighed amounts of the components. [c] Quantum yield for monodeuterium incorporation (formation of the corresponding monodeuterated products). [d] Quantum yield for loss of deuterium (formation of **1**). [e] Total quantum yield for formation of **4** and **15** from **1** carried out in aqueous D_2SO_4.

deuterium incorporation takes place meta to the position of ipso substitution in the primary photoproduct **15**. Incorporation of the second deuterium is due to deuterium exchange of **15** without ipso substitution.

The extent of deuterium incorporation in **4** was followed as a function of conversion since this would provide some relevant data with regards to the mechanism of the substitution process. Substrate **3** was photolyzed in 2:1 10% D_2SO_4–CH_3CN to various conversions (10–40%, as measured by formation of **4** and **5**) and the product mixtures analyzed by GC/MS for isotopic abundances in substrate **3** and in primary photoproduct **4**. As expected, % deuterium incorporation increased with increasing conversion for **3**, from 0% before photolysis, to ≃30% after 30 min. *However, the monodeuterium content of* **4** *was independent of conversion at 65 ± 5%*. This result requires that a protonated species be a precursor to the ipso substitution product **4**, which has already been suggested by acid catalysis of the reaction.

Quantum Yields. Quantum yields for formation of the corresponding monodeuterium products of **1**–**3**, formation of **1** from **6** and formation of **4** from **3** were measured as a function of medium acidity (8:2 aqueous D_2SO_4-(H_2SO_4)–CH_3CN; λ_{ex} = 254 nm; potassium ferrioxalate actinometry[12]). All conversions were kept below 20%. The results are shown in Table I.

All quantum yields increased with increasing acidity. Quantum yields for loss of deuterium label of **6** are very similar to the quantum yield for incorporation of deuterium for **1** at low acidity. However, at higher acidity, the quantum yields for **1** are substantially higher. This would be expected since there is a primary isotope effect which favors removal of H vs D in the cyclohexadienyl cation intermediate, which is identical for both compounds. This isotope effect is very close to unity at low acidity, suggesting that the transition state for deprotonation is very early, which would be reasonable since the cyclohexadienyl intermediate would be highly reactive at these low acidities. Additional studies confirming the dependence of lifetime of the cyclohexadienyl intermediate on acidity would be highly desirable but is unavailable at present.

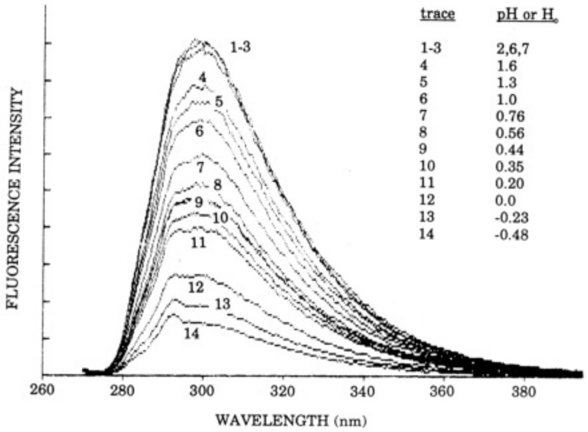


Figure 6. Quenching of fluorescence emission of 1,3-dimethoxybenzene (**1**) by acid ($\Phi_f°$ is the fluorescence quantum yield at pH 7).

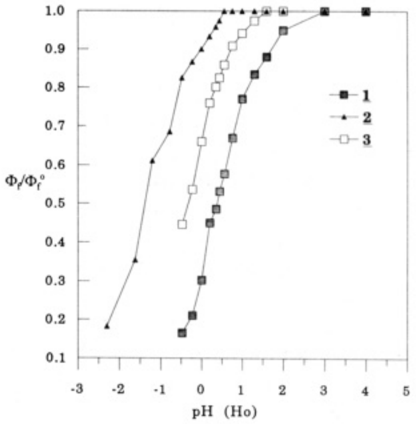


Figure 7. Plot of relative fluorescence quenching efficiency of **1**–**3** as a function of medium acidity ($\Phi_f°$ = fluorescence quantum yield at pH 7).

Quantum yields for exchange of **2** and **3** increase smoothly with increasing acidity. However, the quantum yield for formation of **4** (from **3**) has a steeper dependence at higher medium acidity (the yields rise dramatically between pD = 0.75 and 10% D_2SO_4). Since we have demonstrated above using deuterium labeling experiments that the same cyclohexadienyl intermediate formed via photoprotonation of **3** is reponsible for both exchange and ipso substitution product **4**, the steeper increase in quantum yield of formation of **4** is consistent with changes in reactivity (i.e., partitioning) of the cyclohexadienyl intermediate with acidity.

Fluorescence Measurements. Fluorescence emission spectra of **1**–**3** and **6** were measured as a function of medium acidity in wholly aqueous medium using a Perkin-Elmer MPF 66 instrument at ≃10^{-4} M. Fluorescence emission from all of **1**–**3** and **6** were quenched on increasing acidity, as shown in Figure 6 for **1**. A plot of fractional fluorescence quenching vs acidity is shown in Figure 7. The fluorescence quenching curve for **6** was found to be identical to that observed for **1** (no isotope effect was observable). Much weaker acids were required to significantly quench the emission of **1** while **2** required the use of the strongest acids to effect similar quenching.

Absolute fluorescence quantum yields were measured in 8:2 H_2O–CH_3CN (water portion at pH 7) using anisole

---

(12) (a) Hatchard, C. G.; Parker, C. A. *Proc. R. Soc.* (*London*) **1958**, *A235*, 518. (b) Murov, S. L. *Handbook of Photochemistry*; M. Dekker: New York, 1973.

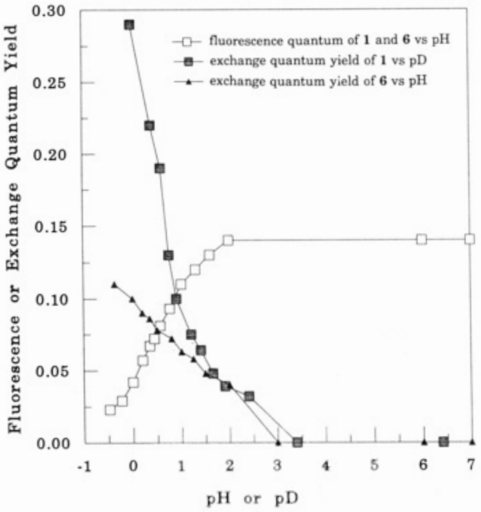


Figure 8. Complementary dependence of exchange and fluorescence quantum yields vs acidity for **1** (vs pD) and **6** (vs pH) (fluorescence quantum yields for **1** and **6** were identical at all pH measured).

(Φ_f = 0.29 in cyclohexane)[13] as external standard. This gave $\Phi_f = 0.14 \pm 0.02$ for all of **1**, **3**, and **6**, and $\Phi_f = 0.15 \pm 0.02$ for **2**. A fluorescence quantum yield of 0.10 ± 0.02 for **2** was obtained using naphthalene as external standard (Φ_f = 0.23 in cyclohexane).[14] Due to poor spectral overlap in absorption spectra, naphthalene could not be used as a standard for **1**, **3**, and **6**.

Shown in Figure 8 is a composite plot of the fluorescence quantum yield of **1** and **6** vs pH (H_o) (which are identical experimentally), and the corresponding exchange quantum yields for **1** (to form **6**; in aqueous D_2SO_4) and **6** (to form **1**; in aqueous H_2SO_4). Although acidities of aqueous H_2SO_4 and aqueous D_2SO_4 solutions are slightly different at the same pH(D) or $H_o(D_o)$ value, the strong complementary dependence of fluorescence quenching and acid catalysis of exchange strong supports a singlet state mechanism for reaction. The exchange quantum yield of **1** (to form **6**) significantly exceeds that of the maximal fluorescence quantum yield (Φ_f = 0.14) at higher acidities. This is quite reasonable since if the mechanism involves competition for the singlet state by proton, the protonation pathway competes with all other deactivational routes, not just with k_f. Quantum yields could not be reliably measured for **1** (or **6**) at higher acidities due to a competing thermal exchange reaction. However, quantum yields for exchange of **2** and **3** (which are much less reactive in the ground state) continue to increase at acidities above 10% D_2SO_4 (the highest acidity quoted in Table I).

Although it is unlikely that equilibrium in the excited state is achieved in the photoprotonation process, the sigmoid type plots observed (Figures 7 and 8) suggest that the excited state (S_1) pK_{BH+} of these compounds is in the range +1 to −2, making them vastly more basic than their corresponding ground states.

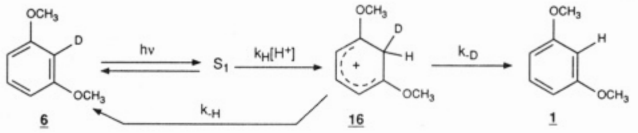
Fluorescence lifetimes of **1**–**3** and **6** ($\simeq 10^{-5}$ M) were measured in wholly aqueous solution at pH 7 using single photon counting on a Photon Technology International LS-1 instrument. Good first-order decays were observed for all runs. All lifetimes were short: **1** (1.5 ± 0.2 ns); **2** (1.7 ± 0.2 ns); **3** (1.3 ± 0.2 ns); **6** (1.5 ± 0.2) (Table II). Lifetimes of **1** were also measured as a function of medium acidity and found to decrease with increasing acidity. For example, at pH = 0.8, $\tau \simeq 1$ ns. Due to the limit imposed by the pulse width of the H_2 spark lamp used (typically 2–3 ns), lifetimes below 1.0 ns with reliable χ^2's were not obtainable with our apparatus. However, the decrease in fluorescence lifetimes with acidity supports a dynamic quenching process of S_1 by proton.

Table II. Summary of Photoprotonation (Fluorescence Quenching) Rate Constants

compound	τ^a	Φ^b	$k_H{}^c$ (M^{-1} s^{-1})	$k_D{}^d$ (M^{-1} s^{-1})
1	1.5 ± 0.2	0.14 ± 0.02	$(2.2 \pm 0.2) \times 10^9$	$(1.5 \pm 0.1) \times 10^9$
2	1.7 ± 0.2	0.15 ± 0.02	$(9 \pm 1) \times 10^7$	–
3	1.3 ± 0.2	0.14 ± 0.02	$(6.0 \pm 0.5) \times 10^8$	–
6	1.5 ± 0.2	0.14 ± 0.02	$(2.2 \pm 0.2) \times 10^9$	–

[a] Fluorescence lifetime in pH 7 (100% H_2O) as measured by single photon counting. [b] Fluorescence quantum yield in 8:2 H_2O–CH_3CN (phosphate buffer at pH 7). [c] Photoprotonation rate constant equated to Stern–Volmer quenching (by proton) carried out in aqueous H_2SO_4. [d] Photodeuteration rate constant equated to Stern–Volmer quenching (by deuteron) carried in aqueous D_2SO_4.

Scheme I



Mechanism. Fluorescence quenching (both steady state and lifetime measurements) and catalysis of reaction by acid indicate that the primary photochemical step for reaction of all compounds is protonation of the aromatic ring, to give cyclohexadienyl cation intermediates. Recent laser flash photolysis studies of several substituted benzenes including 1,3-dimethoxybenzene (**1**) in HFP by McClelland and co-workers[7b,c] have shown that cyclohexadienyl cations are indeed formed in this acidic but non-nucleophilic medium. In the case of **1**, exclusive photoprotonation of the 2-position (to give **16**) was demonstrated by transient absorption (λ_{max} = 410 nm; k(decay) = 4.2×10^3 s^{-1} in HFP) and ^1H NMR studies of the exchanged photoproduct in HFP-O-*d*. Our results in aqueous acid media corroborate these initial findings. Moreover, fluorescence quenching data (which cannot be obtained in HFP) provide a direct measure of the rate of photoprotonation and product quantum yield data provide a measure of the relative partition rates of the photogenerated cyclohexadienyl cations. In addition, product studies of the 1,2-isomer **3** revealed a new reaction pathway of the corresponding photogenerated cyclohexadienyl cation.

The proposed mechanism of photoexchange for **1**, **2**, and **6** is shown in Scheme I using **6** for illustrative purposes. The primary photochemical step is protonation of the aromatic ring of S_1 (to generate cyclohexadienyl cation **16**), resulting in fluorescence quenching. Stern–Volmer plots of fluorescence quenching by proton are linear (Figure 9) and it seems reasonable with the available data that these are equatable to k_H, the photoprotonation rate constant (Table II). In aqueous D_2SO_4, the corresponding rate constant is k_D. Loss of proton (k_{-H}) leads back to **6**. Loss of deuteron (k_{-D}) gives exchanged product **1**. The 1,3-isomer **1** (**6**) is the most reactive towards photoprotonation, with 1,4-dimethoxybenzene (**2**) being the least reactive, as measured by k_H values. There is a small isotope effect when D^+ is used as the quencher ($k_H/k_D \simeq 1.5$ for **1**), which is not unexpected since the rates are so large to begin with. This magnitude of the isotope effect (which

---

[13] Berlman, I. B. *Handbook of Fluorescence Spectra of Aromatic Molecules*; Academic Press: New York, 1971.

[14] Eaton, D. F. *Pure Appl. Chem.* **1988**, *60*, 1107.

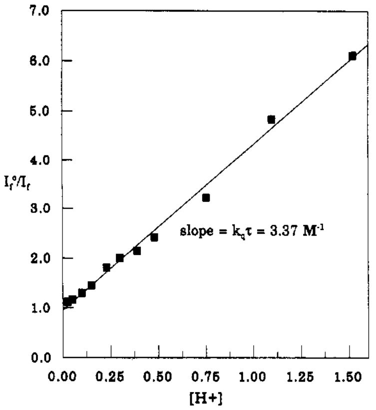


Figure 9. Typical Stern–Volmer plot of fluorescence quenching ($I_f°/I_f$) by proton for 1 ($I_f°$ = fluorescence emission intensity at pH 7).

is in fact a primary one) is consistent with an early transition state for the photoprotonation reaction.

The relative magnitudes of k_H observed for 1–3 presumably reflect the relative basicity (electron density) of these positions in the excited state. Although each of 1–3 is a different compound and hence other factors could explain the different k_H's observed, it is interesting to note that the observed trend in k_H could have been predicted using data from our studies of the photosolvolysis of isomeric dimethoxybenzyl alcohols.[4f,g] In these studies, it was found that with respect to enhancing photosolvolysis, the electron releasing effect of methoxy substituents was essentially additive. For example, the compound with two *o*-methoxy substituents was found to be the most activating for benzyl alcohol photosolvolysis, followed by the compound with *o*- and *m*-methoxy substituents. On the basis of the results of these studies, the 2-position of 1,3-dimethoxybenzene (1) would be expected to be most activated (or most basic). The 3-position of 3 would be predicted to be more basic than the 4-position but still less reactive than the 2-position of 1, both of which have been confirmed.

The regioselectivity of photoprotonation of 1 may also be rationalized with simple HMO theory. Using standard HMO parameters for oxygen, calculations gave five HMO's that are bonding and three antibonding. With the assumption that each oxygen will utilize two valence electrons in the π system, all five bonding HMO's are occupied. Considering only the HOMO and LUMO (Ψ_5 and Ψ_6, respectively), it is clear that promotion of an electron from Ψ_5 to Ψ_6 will result in a decrease of electron density at carbons 3 and 4 and at oxygen and an increase at carbons 2 and 5 (Figure 10). Facile photoprotonation at position 2 has already been demonstrated and there is evidence to suggest that position 5 is also photoprotonated but much less efficiently than position 2. Similar HMO results have been obtained for 2 and 3. Simple HMO calculations used to predict the direction in change of electron density of several dimethoxybenzenes in the excited state have also been made by Smith,[5g] the results of which corroborate these findings.

At pH 1, the quantum yield for formation of 16 (from 6) is calculated to be 0.22 assuming τ = 1 ns at this acidity. However, the exchange quantum yield (formation of 1) is 0.063 at this pH. This implies that only 29% of 16 goes on to form 1 (via loss of D; k_{-D}); the majority of 16 reacts via loss of H (k_{-H}) to give back 6. This data works out to give a primary isotope effect for deprotonating the cyclohexadienyl cation 16, $k_{-H}/k_{-D} \simeq 2.5$ at pH 1.

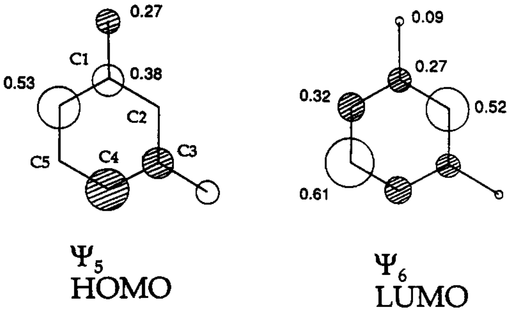


Figure 10. Hückel molecular orbitals Ψ_5 (HOMO) and Ψ_6 (LUMO) of 1,3-dimethoxybenzene (1) (shaded orbitals indicate positive sign of HMO coefficient; numerals indicate absolute magnitude).

The proposed mechanism for deuterium exchange and ipso substitution of 3 is shown in Scheme II. The primary photochemical step is protonation of 3 at the 3-position, to generate cyclohexadienyl cation 17. Loss of deuteron leads back to 3. Loss of proton gives the observed deuterium exchanged product 11. The ipso product must arise via nucleophilic attack of water at the ring carbon bearing the methoxy group furthest away from the site of deuteration (protonation). This position is also "meta" to the site of deuteration. That this site should be more electron deficient than the "ortho" site implies "meta" activation by this methoxy group. Zimmerman and Sandel[15] originally used this concept to rationalize the enhanced solvolytic reactivity of *m*-methoxybenzyl acetates over the para isomer. It appears that this phenomenon is now manifested in the regiochemistry of the observed ipso substitution. To our knowledge, this is the only example in which the isolation of a photoproduct suggests the involvement of meta activation of the methoxy group in the excited state.

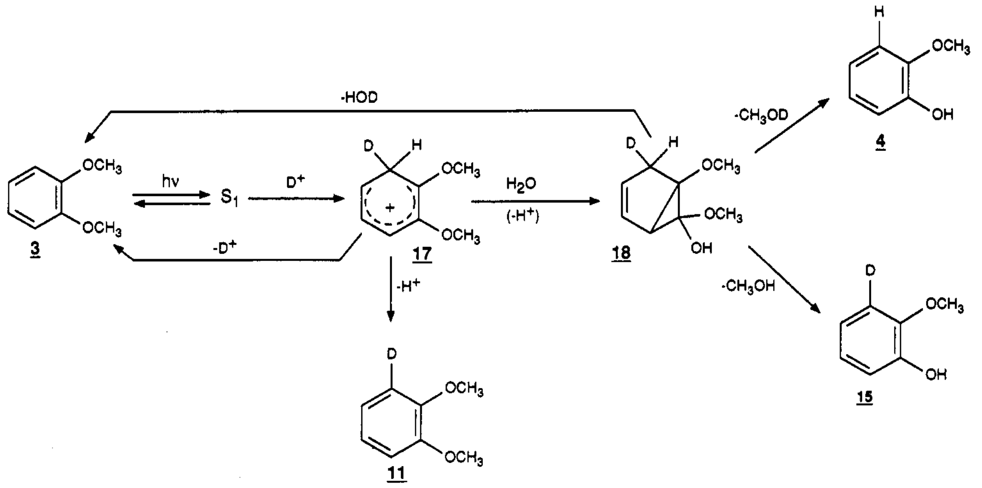
Since 3 is not known to react via ipso substitution under thermal conditions, even in very strong acid (only deuterium exchange takes place), it is clear that when 17 is generated thermally, nucleophilic attack by H_2O is not a viable pathway. Therefore, we propose that the photochemical mechanism most likely involves attack of H_2O on an electronically or vibrationally excited 17, to give 18. Loss of HOD from 18 leads back to 3. Loss of CH_3OD and CH_3OH leads to 4 and 15, respectively. This pathway is consistent with the finding that the ratio 4:15 (= 35:65) is essentially independent of conversion and simply reflects the primary isotope effect (k_H/k_D = 1.8) for loss of $CH_3OH(D)$ from 18. The probable existence of intermediate 18 is further supported by the lower than expected exchange quantum yields observed for 3: at the same acidity, the quantum yield of exchange is higher for 2 than for 3 although k_H is 1 order of magnitude larger for 3. These observations are reconciled by the mechanism shown in Scheme II. Intermediate 17 has a competing step not available to the corresponding intermediate from 2, viz. nucleophilic attack by H_2O, which must be an important competing pathway since the quantum yield for formation of 4 surpasses that of deuterium exchange at 10% D_2SO_4.

An alternative mechanism for formation of 4 is shown in Scheme III in which initial photoprotonation takes palce at the ipso position. Although it is not possible to rule out this pathway with the data available, it is at best a competing pathway since Scheme III cannot account for deuterium incorporation in 4. In addition, the steric

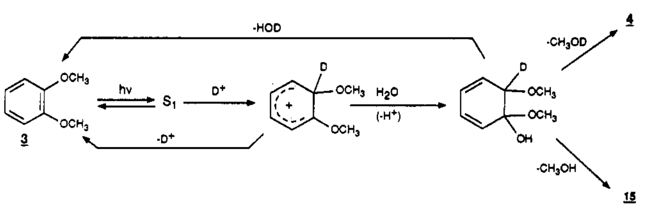
---

[15] Zimmerman, H. E.; Sandel, V. R. *J. Am. Chem. Soc.* **1963**, *85*, 915.

Scheme II



Scheme III



hindrance associated with ipso protonations would also tend to make this pathway less attractive.

The question remains as to why only **3** (the 1,2-isomer) reacts via the ipso substitution pathway. Although no completely satisfying explanation is available at this time, the apparent requirement of a methoxy group meta to the site of photoprotonation is necessary, which is not satisfied in **1** but is so in **2** (the 1,4-isomer). No ipso product was detectable in the photolysis of **2** in the acids used. However, a major difference between **2** and **3** is in their relative rates of photoprotonation: **3** is about 1 order of magnitude more reactive based on k_H (Table II). This difference may account for the failure to observe the ipso substitution process in **2** since photolysis runs of this substrate were never taken to high conversions due to its much lower reactivity to photoprotonation. Finally, the presence of an adjacent methoxy group in **3** may provide an additional activating influence for ipso substitution which is not available in **2**. Additional mechanistic studies of acid-catalyzed ipso substitution of alkoxy groups in S_1 is continuing in our laboratory.

Experimental Section

General. Preparative photolyses were carried out using an Rayonet RPR 100 photochemical reactors equipped with 16 × 254 nm lamps. ^{1}H NMR spectra were taken in $CDCl_3$ on Perkin-Elmer RS32 (90 MHz), Bruker WM 250 (250 MHz) or AM 360 (360 MHz) instruments. Gas chromatography was carried out on a Varian 3700 instrument with a Hewlett-Packard 3390A integrator using a DB-5 capillary column. Mass spectra were taken on Finnigan 3300 or Kratos Concept H (EI and CI) instruments (EI mode). Aqueous acids used either commercially available phosphate buffer solutions or freshly made aqueous H_2SO_4 solutions diluted from standardized stock. Aqueous D_2SO_4 solutions were made by diluting commercially available concd D_2SO_4, and the pD values were calculated by the equation[16] pD = pH(meter) + 0.040.

Materials. Dimethoxybenzenes **1**–**3** were purchased from Aldrich and used as received after purity checks by GC indicated >98% purity. Commercially available guaiacol (**4**) and catechol (**5**) were used for confirmation of product formation, by GC coinjection and comparison of ^{1}H NMR spectra.

1,3-Dimethoxybenzene-2-*d* (6). To a stirred solution of **1** (4 g, 0.0288 mol) in 100 mL of dry THF was added dropwise 35 mL of n-BuLi (2.5 M in hexanes) under N_2 with stirring. The mixture was refluxed under N_2 for 2 h and quenched with 10 mL of D_2O. Extraction with CH_2Cl_2 and subsequent evaporation of the solvent gave an orange oil that was purified by bulb to bulb distillation, ^{1}H NMR δ 3.78 (s, 6 H, OCH_3), δ 6.51 (d, J = 8 Hz, 2 H, H4), δ 7.17 (t, J = 8 Hz, 1 H, H5). The ^{1}H NMR was identical in all respects to that of **1** except with the absence of the two-proton resonance and its associated couplings; MS (EI) m/z (rel inten) 139 (M^+) (100), 110 (15), 95 (20).

Product Studies. In general, 50–60-mg samples were dissolved in the appropriate solvent or solvent mixture (50–100 mL) and irradiated in 100-mL quartz tubes. Solutions were cooled using a cold-finger (tap water) along with continuous purging with a stream of argon via a long fine metal needle.

Photolysis of 1 and 2 in Aqueous D_2SO_4–CH_3CN. A solution of **1** (50 mg, 60 mL 2:1 10% D_2SO_4–CH_3CN) was irradiated at 254 nm for 30 min. After photolysis, 50 mL of H_2O was added, and the solution was extracted with 3 × 100 mL of CH_2Cl_2. The combined extracts were dried over $MgSO_4$ and evaporated. Product analysis were carried out by using ^{1}H NMR and GC/MS: ^{1}H NMR δ 3.78 (s, 6 H, OCH_3), δ 6.45 (t, J = 3 Hz, 1 H (60% deuterium incorporation), H2), δ 6.51 (d, J = 8 Hz, 2 H, H4), δ 7.17 (t, J = 8 Hz, 1 H, H5); GC/MS (CI) m/z (rel inten) 139 (M^+ + 1) (40), 140 (M^+ + 2) (60).

Photolysis of **1** was also carried out at 254 nm for 2 h. After workup (procedure described above), the product mixture was analyzed by ^{1}H NMR and GC/MS. Product **6** was identified by ^{1}H NMR δ 3.78 (s, 6 H, OCH_3), δ 6.51 (d, 2 H, H4) and δ 6.51 (s, 2 H, H4), δ 7.17 (t, 1 H, H5). Since the δ 6.45 triplet has completely disappeared in this run, the conversion to **6** was very high (>90%). However, the product mixture in this extended run was contaminated with thermal exchange products, as demonstrated by control dark runs.

Compound **2** (57 mg) was irradiated in 60 mL of 2:1 20% D_2SO_4–CH_3CN at 254 nm for 1 h. After workup (procedure described above), the product mixture was analyzed by ^{1}H NMR and GC/MS: ^{1}H NMR δ 3.76 (s, 6 H, OCH_3), δ 6.83 (d, J = 8 Hz, 4 H (20% deuterium incorporation), H2); GC/MS (CI) m/z (rel inten) 139 (M^+ + 1) (80), 140 (M^+ + 2) (20). A dark control reaction for **2** with the above conditions gave unreacted starting material as shown by ^{1}H NMR and GC/MS. Photolysis of both **1** and **2** in 2:1 aqueous H_2SO_4–CH_3CN was also carried out. Analysis of these runs by GC and ^{1}H NMR showed that both starting materials were left unchanged.

Photolysis of 3 in Aqueous H_2SO_4–CH_3CN. A solution of 55 mg of **3** in 60 mL of 2:1 10% H_2SO_4–CH_3CN was irradiated at 254 nm. At selected time intervals, 2-mL samples were withdrawn for analysis. Each sample was diluted with about 3

---

[16] Bates, R. G. In *Determination of pH-Theory and Practice*; Wiley: New York, 1973.

mL of H_2O, NaCl was added, and the solution was extracted 3× with CH_2Cl_2. The combined extracts were dried over $MgSO_4$ and evaporated. Percent conversion to products 4 and 5 vs time was determined by GC (Figure 1) and the structures of these photoproducts were confirmed by GC/MS and coinjection with authentic materials.

Photolysis of 3 in Aqueous D_2SO_4–CH_3CN. Isolation and Characterization of 11. Seven separate batches of 50 mg of 3 were irradiated in 45 mL of 2:1 10% D_2SO_4–CH_3CN at 254 nm for 90 min each. The runs were combined together, diluted with H_2O, and extracted 3 × 100 mL of CH_2Cl_2. The organic layers were combined and a GC was taken to determine % conversion to products, which showed 3 + 11 (24%), 4 (29%), and 5 (43%). Then the combined CH_2Cl_2 extact was washed with 0.1 M NaOH to remove the two phenols (4 and 5) and dried over $MgSO_4$ and evaporated. The resulting material was purified by preparative TLC (silica, 1:1 CH_2Cl_2–hexanes) and its structure was confirmed by ^1H NMR, ^{13}C NMR, and GC/MS to be a mixture of 3 (70%) and 11 (30%) (see text).

Isolation and Characterization of 15. A solution of 50 mg of 3 was irradiated in 60 mL of 2:1 10% D_2SO_4–CH_3CN at 254 nm for 15 min. After photolysis, the solution was diluted with H_2O and extracted 3 × 100 mL of CH_2Cl_2 and a GC was taken, which showed 17% conversion to 4 + 15. The phenol products 4 and 15 were separated from 3 by extraction with 0.1 M NaOH. The aqueous layers were combined and acidified with concd HCl, NaCl was then added, and 4 and 15 were extracted out with 3 × 100 mL of CH_2Cl_2. The material was further purified by preparative TLC (silica, 1:1 CH_2Cl_2–hexanes). The phenol mixture was then dissolved in CH_2Cl_2 and reacted with 0.47 g (0.0046 mol) of acetic anhydride and 0.80 g of K_2CO_3 (stirred for 3.5 h at room temperature). After reaction, the solution was extracted once with 5% K_2CO_3, washed 2× with 0.1 M NaOH, dried over $MgSO_4$, and evaporated. The presence of both 12 and 13 as major products was confirmed by GC/MS and ^1H NMR (see text): GC/MS (CI) *m/z* (rel inten) 167 ($M^+ + 1$) (63), 168 ($M^+ + 2$) (12).

The above experiment was repeated several times with different photolysis times, to give different conversions (10–40%, as measured by formation of 4 by GC). The product mixtures were worked up as above and the extent of deuterium incorporation in 3 and 4 was analyzed as a function of conversion by GC/MS.

Thermal Exchange of 1 in Aqueous D_2SO_4–CH_3CN. Compound 1 (55 mg) in 60 mL of 2:1 10% D_2SO_4–CH_3CN was stirred in the dark for 30 min. Workup was as described above for the corresponding photolysis run for 1. The product mixture was characterized by ^1H NMR and was shown to contain both 8 and 9: ^1H NMR δ 3.78 (s, 6 H, OCH_3), δ 6.45 (t, $J = 3$ Hz, 1 H, H2), δ 6.51 (d, $J = 8$ Hz, 2 H, (5–10% monodeuterium incorporation), H4), δ 7.17 (t, $J = 8$ Hz, 1 H, H5). The signal at δ 7.17 also has a superimposed singlet indicating presence of 9 and a doublet indicating presence of 8.

Quantum Yield Measurements. Quantum yields were measured using a Rayonet RPR 100 photochemical reactor (16 × 254 nm lamps). Solutions ($\simeq 10^{-3}$ M) were prepared in 3.0-mL quartz cuvettes and purged with a stream of argon prior to photolysis. Potassium ferrioxalate was used for chemical actinometry.[12] After photolysis, the sample was extracted several times with CH_2Cl_2 and conversions (kept <20%) analyzed by GC and/or GC/MS.

Fluorescence Measurements. Fluorescence emission spectra (uncorrected) were taken in 3.0-mL quartz cuvettes at $\simeq 10^{-4}$ M using a Perkin-Elmer MPF 66 spectrophotometer at ambient temperature (λ_{ex} = 265 nm). Samples for fluorescence measurements were initially deaerated by argon purging prior to measurement. However, this had no measurable effect on fluorescence emission yields or lifetimes. Subsequently, all samples were used without deaeration. Fluorescence quenching experiments were carried out by injecting a known volume (typically 10–20 μL) of a stock solution of the substrate dissolved in CH_3CN using a microlitre syringe into a 3.0-mL solution of the appropriate acidity. The cuvette is then shaken and the fluorescence spectra taken. For fluorescence quantum yield measurements, optical densities at λ_{ex} = 265 nm were matched with the external standard prior to measurement. Fluorescence lifetimes were measured at room temperature on a standard single photon counting instrument (PTI LS-1 spectrofluorimeter equipped with single photon electronics) using a hydrogen spark lamp as excitation source. Decays were analyzed using software supplied by PTI.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council (NSERC) of Canada for support of this research in the form of a research grant and a summer scholarship to R.P. We thank Deepak Shukla for carrying out some of the lifetime measurements.