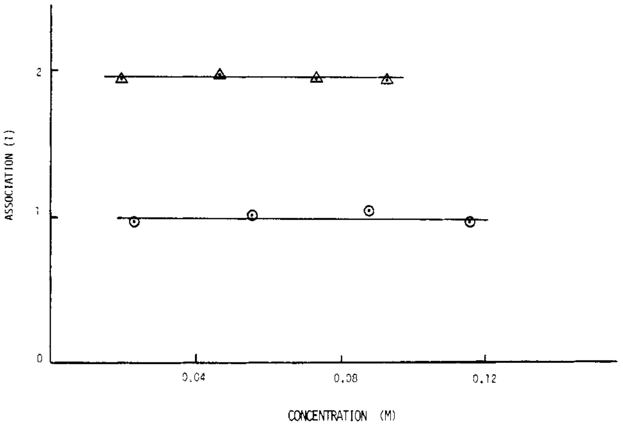

Figure 2. Molecular association studies for $CuMgMe_3$ (⊙) and Cu_2MgMe_4 (△) in THF.

proximately −50 °C, this exchange can be stopped where splitting of the signals is observed (Table II). The spectra at −85 °C show sharp signals. A variable-temperature spectral study on Cu_2MgMe_4 is shown in Figure 1. Addition of magnesium halide ($MgCl_2$ or $MgBr_2$) solution in THF to these reaction mixtures did not affect the proton NMR, indicating no possible interaction of MgX_2 with methylmagnesium cuprates.

In order to ascertain the absence of an exchange process, dimethyl ether was introduced at −120 °C where no further splitting in the signals was observed.

Upon analysis of the variable-temperature proton NMR data, it appears that the solutions containing higher amounts of organocopper in solution show signals at lower positions than that of higher organomagnesium species. This may be due to the probable formation of bridging methyl groups in the higher copper-containing complexes. This is consistent with the similar behavior observed by us in the system of methyllithium with methylcopper.[15] Although these variable-temperature NMR studies indicate the formation of various complexes in the reactions of methylmagnesium complexes with methylcopper(I) or cuprous halides in various stoichiometries, on the basis of this information it would be very risky to propose structures for these complexes. It is due to the fact that these magnesiummethyl cuprates may exist in ionic form or may be in the form of copper clusters as proposed earlier in the case of Cu_4MgPh_6[16] and recently determined by X-ray crystallography.[17]

In order to learn more about these complexes, molecular association studies in dilute THF solutions were carried out. Ebullioscopic molecular association studies performed under reduced pressure in THF reveals that $CuMgMe_3$ is monomeric whereas Cu_2MgMe_4 is dimeric (Figure 2). Molecular weights of the other complexes could not be carried out successfully due to their thermal instability above 0 °C.[14]

In conclusion, we have shown that various THF-soluble magnesium methylcuprates are formed when methylmagnesium compounds are allowed to react with methylcopper or cuprous halides in THF at temperatures ranging from −78 to −30 °C. Proton NMR spectral studies indicate no involvement of halides in these complexes. Some of these magnesium methylcuprates $Cu_nMg_mMe_{2m+n}$ (where $n = 1$ or 2 and $m = 1$) are stable even at room temperature for some time. Although, no interaction of halides has been observed in our studies, we do not imply that solutions of these complexes with and without halides would react with organic substrates such as alkenes and alkynes in exactly the same way and at the same rate, since the halides may have some interaction with the organic substrates under the reaction conditions.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

Registry No. CuBr, 7787-70-4; CuCl, 7758-89-6; MeCu, 1184-53-8; CuI, 7681-65-4; MeMgCl, 676-58-4; MeMgBr, 75-16-1; Me_2Mg, 2999-74-8.

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[15] Ashby, E. C.; Watkins, J. J. *J. Chem. Soc., Chem. Commun.* **1976**, 784.

[16] Parker, V. D.; Piette, L. H.; Salinger, R. M.; Noller, C. R. *J. Lam. Chem. Soc.* **1964**, *86*, 1110. Costa, G.; Camus, A.; Gatti, L.; Marsich, N. *J. Organomet. Chem.* **1966**, *5*, 568. Seitz, L. M.; Madl, R. *Ibid.* **1972**, *34*, 415.

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Selectivity in the Metalation of Polymethylpyrazines

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Philip Morris U.S.A. Research Center, Richmond, Virginia 23261

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The selectivity in the LDA-promoted lithiation of 2,3,5-trimethylpyrazine was studied by using the perdeuterated substrate 1-d_9. Quenching of the lithium salts of the latter with H_2O gave a 1-d_8 isomer mixture which was analyzed by NMR. The order of reactivity of the three CH_3 groups in 1-d_9 was found to be 3 > 2 > 5. The metalation studies were extended also to isomeric dimethylpyrazines. It was established that the two ortho CH_3 groups in 2,3-dimethylpyrazine are more easily metalated than either of the CH_3 groups in the other isomeric dimethylpyrazines.

Alkylpyrazines are easily metalated by lithium amides such as lithium diisopropylamide (LDA), and the resulting anions are useful intermediates in the syntheses of a variety of pyrazine derivatives.[1] When 2,3,5-trimethylpyrazine (1) is reacted with an organolithium reagent, three different anions can be formed (**1a–c**, Scheme I). Hence, when such a mixture is treated with a reagent, the formation of three different products could be expected. A few reported examples, however, suggest that this assumption is incorrect. Rizzi[2] reported that the reaction

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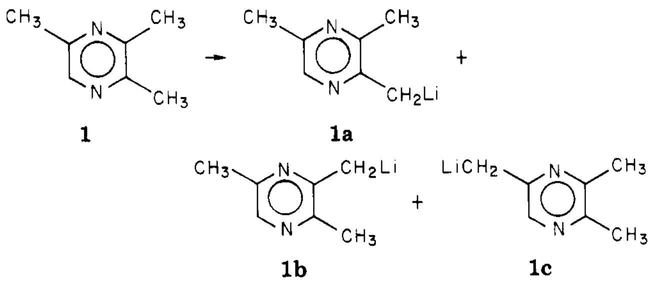
[1] Cheeseman, G. W. H.; Werstiuk, E. S. G. *Adv. Heterocycl. Chem.* **1972**, *14*, 99.

[2] Rizzi, G. P. *J. Org. Chem.* **1968**, *33* 1333. In this case, methyllithium leads exclusively to side-chain metalation.

0022-3263/83/1948-2130$01.50/0

Scheme I



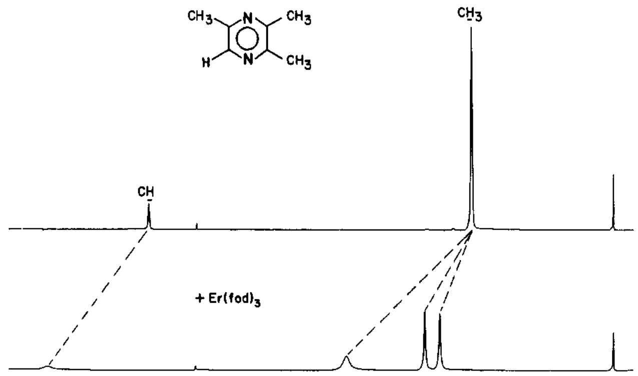
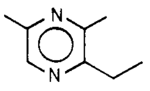


Figure 1. Separation of pyrazine methyl resonances by using shift reagents.

of 1 with methyllithium, followed by dimethyl sulfate, gave only two of the three possible isomers of dimethyl ethylpyrazine, 2 and 3, respectively. No trace of the other possible isomer 4 was observed in the crude reaction product. We have recently reported[3] that treatment of 1 with LDA followed by *trans*-1,2-dichloroethylene gave only two pyrrolo[1,2-*a*]pyrazines, 5 and 6 in about a 1:2 ratio, resulting from the reaction of 1a and 1b, respectively. Here again, the third possible isomer 7 could not be detected in the crude reaction mixture. The above observations prompted us to study in more detail the selectivity in the metalation of 2,3,5-trimethylpyrazine. This study was also extended to isomeric dimethylpyrazines.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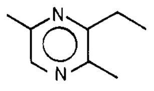
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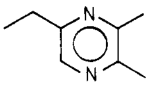
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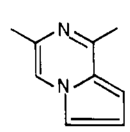
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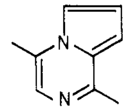
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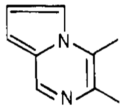
7

Results and Discussion

When a metalated mixture of 1 is quenched with a reagent, the distribution of products may be affected by steric factors dependent on the reagent's size. To minimize this possibility, we have studied the metalation of 1 by quenching its anion mixture with D_2O and have measured the distribution of deuterium in the product by NMR.

In the ^1H NMR spectrum of 1 taken in all common NMR solvents, the three CH_3 group resonances overlap. However, the use of lanthanide shift reagents (LSR) allows the CH_3 resonances to be separated and subsequently assigned. Figure 1 shows the ^1H spectra of 1 taken in $CDCl_3$ with and without $Er(fod)_3$, respectively. From the Er-induced-shift ^1H spectrum of 1, it is apparent that the site of coordination of the LSR is through the less sterically hindered N-1. This stands to reason since the steric requirements of LSR's are well documented.[4,5]

Table I. Experimental vs. Calculated Shifts for 1 With $Er(fod)_3$[a]

nucleus	shift, ppm exptl	shift, ppm calcd
C-2	1.56	1.56
C-3	0.49	0.71
C-5	0.43	0.56
C-6	1.29	1.23
2-CH_3[b]	1.29	1.23
3-CH_3[b]	0.34	0.41
5-CH_3[b]	0.27	0.22
H-6	0.65	0.64

[a] Standard deviation 0.15. [b] Carbon nucleus.

Coordination of the LSR through N-1 induces large downfield shifts in the ring proton (H-6) and the CH_3 resonance adjacent to N-1. This large shift in one of the CH_3 resonances allows assignment of the 2-CH_3. The 3- and 5-CH_3 resonances exhibited smaller downfield shifts and could not be assigned from the proton shift data alone. To assign these resonances, we use the ^{13}C Er-induced shifts along with the proton data from H-6 to determine the configuration of the complex by employing a standard molecular geometry analysis technique. This technique fits the induced shift data to a relative substrate–LSR orientation via the pseudocontact equation:

$$\mathrm{LIS} = k(3\cos^2\theta - 1)/r^3$$

In using this equation, we make the usual assumptions of effective axial symmetry and a dominance of pseudocontact interactions. The ^{13}C shift data provided the "skeletal" information needed to fit the geometry of the substrate. The atomic positions were determined from X-ray data of model compounds and standard geometry parameters. A "best fit" lanthanide position was derived by systematically orienting the molecular coordinates of the substrate relative to a fixed lanthanide position chosen to be the origin of the polar coordinate system. The substrate coordinates were varied so that the lanthanide ion remained in the plane of the pyrazine ring. Computer refinement continued until the standard deviation between the experimental and calculated shifts was minimized. The results of this optimization process listed in Table I clearly indicate that the order of the induced shifts of the methyl groups is $2 > 3 > 5$.

Assignment of the resonances of the three CH_3 groups in [1] enabled us to quantitate its metalation. 1 was allowed to react with exactly 1 equiv of LDA in ether at 0 °C. Under these conditions the metalation is instantaneous, and the lithium salts (1a–c) appear as a red suspension as a result of their low solubility in ether. It should be noted also that no ring metalation occurs under these conditions. Quenching of 1a–c with D_2O afforded a mixture of monodeuterated isomers of 1 (1-*d*). Integration of the NMR spectrum of 1-*d*, revealed that loss of H, i.e., exchange, occurred mainly from the 3-CH_3 group. However, the integration ratio of the three CH_3 signals, accounting for the loss of one proton out of nine, was not accurate enough to enable us to quantitate the selectivity

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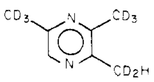
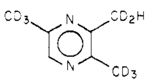
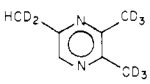
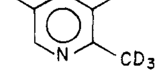
Table II. Distribution of Hydrogen in the Reaction of 1-d_9 with LDA in Ether followed by H_2O

structure			
incorporation of H,[a] %	33	59	8

[a] The accuracies of these determinations are ±3%. H-6 is taken as 100% of 1 H.

in the metalation of 1. To overcome this difficulty a reverse-exchange method was tried: a sample of perdeuterated 1 (1-d_9) was prepared by repeated refluxing of 1 in D_2O containing NaOD. 1-d_9 was treated with LDA as above and than quenched with H_2O. Integration of the NMR spectrum of the resulting 1-d_8 isomer mixture gave an accurate measurement of the distribution of H among the three possible structures as shown in Table II.

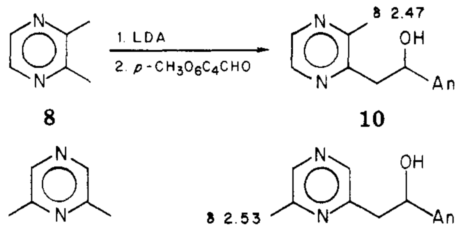

1-d_9

The results in Table II show clearly that the three CH_3 groups in 1 differ remarkably in their acidities. It should be pointed out that because of the very low solubility of the lithium salts 1a–c in ether, it is very unlikely that the results in Table II reflect thermodynamic acidities. It appears that the results reflect kinetic acidities even though it can be argued that at least in part the results may be affected by different precipitation rates of 1a–c. It should be noted that all methylpyrazines generally form insoluble lithium salts when treated with LDA in ether at 0 °C. All of these salts appear to have the same degree of insolubility. Moreover, a low concentration solution of 1-d_9 in THF was treated with LDA at 0 °C, conditions under which the resulting lithium salts are soluble. The solution was quenched with H_2O, and the analyzed products (1-d_8 isomers) were found to have the same distribution as shown in Table II. This clearly indicated that the insolubility of 1a–c in ether is not a major factor affecting these results. Therefore, it is likely that the results in Table II reflect the kinetic acidities of the three CH_3 groups in 1.

The results in Table II are in good agreement with previous observations regarding the distribution of products in the reaction of 1 with LDA followed by different organic reagents.[2,3] The selectivity in the metalation of the three CH_3 groups in 1 is very significant. In particular, it is surprising that the 5-CH_3 group is the least reactive (Table II). On the basis of steric factors it should be the most reactive group since it is less hindered than both the 2-CH_3 and the 3-CH_3 groups. Moreover, considering electronic factors, it should have a reactivity similar to that of the 3-CH_3 group.

It is perhaps most interesting that the selectivity in the metalation of 1 shows some similarity to the selectivity of the n-BuLi-promoted metalation of 1,2,4-trimethylbenzene,[6] even though in the latter case this selectivity is less pronounced. In their extensive study on the metalation of polymethylbenzenes, Klein et al.[6] have found that in 1,2,4-trimethylbenzene the 2-CH_3 group is the most reactive (this corresponds to the 3-CH_3 group in 1). It was also established that two CH_3 groups ortho to each other on an aromatic ring are more easily metalated than two CH_3 groups para to each other.[6] A detailed theoretical discussion of this phenomenon has been presented by Klein et al.[6] The finding that the rate of metalation of a benzylic methyl located ortho is larger than that para to another methyl was reported earlier by others.[6,7] It is very likely that in 1 the enhanced reactivity of both the 2- and in particular the 3-CH_3 groups is caused by the same effects operating in the methylbenzenes. To further study this similarity, we have examined the rate of metalation of dimethylpyrazines. The 2,5-dimethylpyrazine isomer was excluded from this study since it was found that its anion is very unstable and undergoes rapid decomposition and/or self-condensation to produce tar.[8] However, both the 2,3- and 2,6-dimethylpyrazines, 8 and 9, respectively, were found to react smoothly with LDA in ether or glyme, yielding anions of similar stability and thus enabling a comparison of the relative reactivities of the parent dimethylpyrazines. A 1:1 mixture of 8 and 9 was allowed to react with only 1 equiv of LDA in ether at 0 °C (i.e., ratio of total pyrazines to LDA was 2:1). The resulting red suspension was reacted with p-methoxybenzaldehyde according to Scheme II to form the corresponding pyrazinethanols 10 and 11, respectively. The two products which have the same R_f value on TLC were isolated together by preparative TLC, and the NMR of their mixture was taken in $CDCl_3$. Integration of the CH_3 groups of 10 and 11 gave a ratio of 10/11 of 61:39. Similar results were obtained from the integration ratio of the pyrazine protons of 10 and 11. These results clearly demonstrate that 8 is more reactive than 9. To eliminate the possibility that the solubilities of the lithium salts of 8 and 9 are different and therefore affect the results, we carried out the same experiment in glyme where precipitation does not occur. The ratio of 10/11 in that solvent was found to be 74:26, again showing that 8 is much more easily metalated than 9. Moreover, these results establish that the dimethylpyrazines behave similarly to xylenes and that ortho reactivity is much more pronounced in the methylpyrazines. It should be emphasized, however, that the conditions used in our experiments are different from those used with the polymethylbenzenes owing to the much lower acidities of the methylbenzenes. Nevertheless, the polymethylpyrazines and polymethylbenzenes show the same pattern of behavior. This suggests that similar effects are operating in the two systems, thus making the selectivity in the metalation of polymethyl aromatics a general phenomenon extending also to polymethyl diaza aromatics.

Scheme II



9 11

Experimental Section

All reactions involving organometallic reagents were carried out under a N_2 atmosphere. Both qualitative TLC and preparative TLC were carried out on silica gel GF plates with hexane containing 15–40% acetone as the eluent. Column chromatography with hexane containing 5–30% acetone as the eluent was con-

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(6) Klein, J.; Medlik-Balan, A. J. Am. Chem. Soc. 1977, 99, 1473 and references cited therein.

(7) Gau, G.; Marques, S. J. Am. Chem. Soc. 1976, 98, 1538.

(8) Houminer, Y. J. Org. Chem. 1980, 45, 999.

ducted on 60-mesh silica gel. Authentic samples of both **10** and **11** were prepared by a literature procedure.[8]

NMR Studies. The Er(fod)$_3$ was obtained from the Norell Chemical Co. and used without further purification. ^{1}H NMR spectra were recorded on a Bruker WP-80 spectrometer and carbon spectra on a Varian XL-100 spectrometer, both operating at ambient probe temperature. The paramagnetic shifts reported are the slopes of the molar ratio vs. the induced shift plots after extrapolation to a 1:1 molar ratio. Experimental molar ratios ranged from 2×10^{-3} to 3×10^{-2}. Induced shift experiments were done by the incremental addition of shift reagent to the substrate solution, and both ^{1}H and ^{13}C spectra were run on the same sample. The computer analysis was done on a Xerox Sigma IX computer.

Preparation of 1-d_9. 2,3,5-Trimethylpyrazine (3.5 g) in 60 mL of D$_2$O (99.7% D) containing 5 mL of 40% NaOD (99.0% OD) was refluxed under dry N$_2$ for 5 days. The solution was extracted with CH$_2$Cl$_2$, the organic layer dried (MgSO$_4$), and the solvent removed under reduced pressure to give 3 g of the deuterated product. The NMR spectrum indicated that only 91% exchange occurred. The above process was repeated with reflux continuing for only 3 days. A workup as above the distillation gave pure product with 98.6% D (the H-6 is taken as 100% of 1 H). The unexchanged residual protons were determined by integration of the spectrum obtained with Er(fod)$_3$. The following residual protons in the three different CH$_3$ groups were obtained: 2-CH$_3$, 0.018 H; 3-CH$_3$, 0.017 H; 5-CH$_3$, 0.105 H.

Metalation of 1-d_9 with LDA in Ether and in THF. To a solution of LDA (0.01 mol) in ether (80 mL) at 0 °C was added with stirring 1-d_9 (1.31 g, 0.01 mol) in ether (20 mL). The resulting red mixture was stirred at 0 °C for 20 min. Water (H$_2$O) was added (50 mL), the organic layer was separated and dried (MgSO$_4$), and the ether was removed under reduced pressure. Distillation afforded pure 1-d_8. ^{1}H NMR indicated that only 75% of the starting material was metalated. Integration of the spectrum in CDCl$_3$ containing Er(fod)$_3$, after correcting the results for residual protons in the starting 1-d_9, gave the following distribution of proton in 1-d_8: 2-CH$_3$, 0.248 H; 3-CH$_3$, 0.442 H; 5-CH$_3$, 0.062 H. The results are shown in Table II as percent incorporation.

The above experiment was repeated in THF (150 mL). Water was added (100 mL), and the product was extracted with ether (5 × 30 mL). Purification of the product and NMR analysis gave results similar to the above. When the same experiment was carried out at room temperature and the red THF solution was left stirring at this temperature, the red color started to fade after about 8 h.

Metalation of 2,3- and 2,6-Dimethylpyrazines (8 and 9).[8] A solution of **8** and **9** (5.4 g, 0.5 mol of each) in ether (200 mL) was added at 0 °C with stirring to a solution of LDA (0.05 mol) in ether (100 mL). The red suspension was stirred at 0 °C for 20 min. A solution of *p*-methoxybenzaldehyde (6.8 g, 0.05 mol) in ether (40 mL) was added rapidly, and the resulting mixture was stirred for 10 min at 0 °C. Water (50 mL) was added, the ether layer separated, washed with water, and dried (MgSO$_4$), and the solvent removed under pressure. TLC indicated a smooth reaction with mainly products and starting materials present in the crude reaction mixture. A portion of the crude product was separated by preparative TLC, and the two products, **10** and **11**, having the same R_f, were collected. Their ratio was determined by NMR. Complete ^{1}H NMR data for both **10** and **11** have been described in a previous publication.[8]

The above reaction was repeated in glyme as follows. A solution of **8** and **9** (1.08 g, 0.01 mol of each) in dry glyme (30 mL) was added to solution of LDA (0.01 mol) in glyme (70 mL) at 0 °C with stirring. The solution turned red, but no precipitation occurred. The red solution was stirred at 0 °C for 30 min. A solution of *p*-methoxybenzaldehyde (1.36 g 0.01 mol) in glyme (20 mL) was added, and the mixture was stirred at 0 °C for 10 min. Water was added, and the product was extracted with ether. An aliquot was evaporated, and the residue was separated by preparative TLC to give a mixture of **10** and **11** which was analyzed by NMR.

The above experiment was repeated, and the red metalated mixture was stirred at room temperature for 3 h, at which time the red color has almost completely faded. A solution of *p*-methoxybenzaldehyde was added, and the reaction mixture was worked up as above. TLC showed only trace amount of products and mainly unreacted **8** and **9**.

Registry No. 1-d_9, 85735-49-5; 1-d_8 (isomer 1), 85735-50-8; 1-d_8 (isomer 2), 85735-51-9; 1-d_8 (isomer 3), 85735-52-0; **8**, 5910-89-4; **9**, 108-50-9; **10**, 72725-81-6; **11**, 72725-79-2.

Free Radical Oxidations in Water: Decomposition of Azoinitiators and Oxidation of *p*-Cresol and *p*-Isopropylphenol

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The free radical oxidation of *p*-cresol and *p*-isopropylphenol using peroxy radicals produced by thermolysis of azoinitiators in oxygen at 50 °C in purified water is considered. The major primary products of oxidation of *p*-cresol are the peroxycyclohexadienones and the corresponding hydroperoxides; smaller amounts of two phenolic dimers are also found in each case. A variety of other products thought to result from ortho substitution also were observed but not characterized. The general features of the reactions in water are much the same as observed in organic solvents. Cupric ion causes further reaction of the peroxide products, leading to additional oxidation of phenol and possible formation of some *p*-quinone; Fe^{2+} ion in contrast is a strong inhibitor of phenol oxidation by RO$_2$·.

Introduction and Background

Oxidation of phenols by peroxy free radicals (RO$_2$) have been studied extensively both in organic solvents, because of their great importance as inhibitors,[1-3] and in water because of their widespread occurrence as aquatic pollutants.[4,5] The main features of inhibition kinetics are well understood, but the detailed chemistry often remains obscure, owing to the complex chemistry. Because oxidations of phenols in water generally are of interest in connection

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