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# SELECTIVITY OF AROMATIC CHLORINATION REACTIONS WITHIN A REVERSED-PHASE LIQUID CHROMATOGRAPHY COLUMN

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Summary: Substrate selectivity was obtained in the chlorination of a series of *n*-alkyl phenyl ethers by chlorine water on a reversed-phase high performance liquid chromatography column at 25°C.

There have been only a few reports of chemical reactions performed on high performance liquid chromatography (HPLC) columns,[1] and none of them has addressed selectivity. Herein, we report striking substrate selectivity coupled with modest regioselectivity in the chlorination of a series of *n*-alkyl phenyl ethers (1) conducted under HPLC conditions on a reversed-phase column in real-time (*i.e.*, with continuous eluant flow).

Individually and/or in competition runs, ethers 1 were monochlorinated with chlorine water to give 2 and 3[2] on a 25 cm x 4.0 mm (i.d.) column of 10-μm LiChrosorb RP-18 (EM)[3] at 25°C. In a typical experiment, a MeCN solution of one or two ethers was injected at time (t) = 0 onto the column equilibrated with 40% (v/v) MeCN-$H_2O$ at flow rate of 0.5 mL/min, which was maintained throughout the procedure. At t = 5 min, the eluant composition was linearly changed to 100% $H_2O$ (pH 5.5) during 3 min, and at t = 17 min, an aliquot of chlorine water[4] was injected. At t = 20 min, linear gradient elution was begun with MeCN-$H_2O$, which gave resolved 2, 3, and unreacted 1, with UV detection at 254 nm.[5,6]

$$\underset{\underline{1}}{C_6H_5OR} \longrightarrow \underset{\underline{2}}{\underline{p}\text{-}ClC_6H_4OR} + \underset{\underline{3}}{\underline{o}\text{-}ClC_6H_4OR}$$

a, R = $CH_3$    b, R = $C_2H_5$    c, R = $C_3H_7$    d, R = $C_4H_9$
e, R = $C_5H_{11}$    f, R = $C_9H_{19}$    g, R = $C_{12}H_{25}$

The results of individual reactions with 1a, 1e, 1f, and 1g on the column, and with 1a and 1e in 95:5 (v/v) $H_2O$-MeCN under homogeneous conditions are summarized in Table I. For both 1a and 1e, the *para*/*ortho* product ratio (2/3) was greater in the column than in the homogeneous reaction. In the chlorinations of 1e by chlorine water in aqueous micellar sodium dodecyl sulfate and $H_2O$ at 25°C, we found similar ratios of 3.77 and 1.31, respectively.[7] The enhanced *para* regioselectivity was interpreted[7] in terms of polarity effects and greater shielding of the *ortho* positions by the micellar superstructure. Comparable effects probably operate within the $C_{18}$-bonded phase in the column reaction.

In each entry of Table I, 2 and 3 were obtained to the exclusion of the corresponding *n*-alkyl 2,4- and/or 2,6-dichlorophenyl ethers,[2] although they were formed with larger active chlorine/1 ratios. However, the use of lesser ratios in entries 1-4 did not simply result in proportionately smaller yields of 2 and 3. For example, below a ratio of about 10 in entry 1, no chlorination occurred. Furthermore, in entries 1-4, note that a larger value of active chlorine/1 was required to effect reaction with 1a than with the other ethers. Also, its conversion to 2 and 3 without the formation of disubstituted products was considerably higher.

Competition runs with various ether pairs resulted in substantial substrate selectivity in most cases; the results are summarized in Table II. Selective chlorinations of 1e in the presence of 1a, 1b, 1c, and of even closely related homolog 1d were obtained on the column. These results are in marked contrast to the comparable reactivities expected for the members of each pair under homogeneous conditions, as evidenced by the competition (entry 13) and individual runs (entries 5 and 6) with 1a and 1e in 95:5 (v/v) $H_2O$-MeCN. Also, selective reaction of 1f in the presence of 1e was achieved, but there was no selectivity in the competition between 1f and 1g. Also note that the *para*/*ortho* ratios in the competition runs were the same as those in the individual runs.[8]

Chlorine water contains $Cl_2$ and HOCl in equilibrium,[4,9] and both are possible chlorinating agents. For example, with an overall concentration of 0.0329 *M*, those of $Cl_2$ and HOCl are 0.0144 *M* and 0.0185 *M*, respectively.[4] However, the concentration within an aliquot will decrease as it moves through the column due to dilution by the 100% $H_2O$ eluant. The relative amounts of the two species within the aliquot will depend on the overall concentration and on a complex set of undefined factors, including the partitioning of $Cl_2$ and HOCl between the aqueous mobile phase and the $C_{18}$-bonded phase.[10] A control demonstrated that $Cl_2$ is probably the active chlorinating agent. An aqueous 0.020 *M* HOCl solution containing 0.27 *M* $Ag_2SO_4$ and adjusted to pH 1.8 with $HClO_4$[11] was substituted for 0.021 *M* chlorine water, pH 2.1, in the chlorination procedure with 1e; little reaction, if any, was observed.

In view of the relative retention times,[5a,b] the selectivity in the competition runs likely derives at least in part from chromatographic separation of the two ethers on the column. Control runs demonstrated that once the eluant composition has been changed to 100% $H_2O$ in the reaction procedure, the two competing ethers are essentially stationary within the column. However, prior to this immobilization within the $C_{18}$-bonded phase,[12] the more hydrophilic ether (*i.e.*, the shorter chain homolog) has traveled farther down the column. As a result, after its injection, the aliquot of chlorine water encounters and reacts with the more lipophilic ether first.[13] Due to this reaction and to dilution, when the remaining chlorine water reaches the more hydrophilic ether, its concentration is too low to effect chlorination during the limited contact period. Apparently, the chromatographic separation, if any, of 1f and 1g prior to immobilization is insufficient to effect selectivity.

Taken as a whole, the results suggest that the $C_{18}$-bonded phase and/or the bonded phase-aqueous mobile phase interface are possible reactive sites, as opposed to the mobile phase. In addition to chromatographic separation, the substrate selectivity may also involve different solubilization sites for the ethers within the $C_{18}$-bonded phase, to which $Cl_2$ has variable access. The relative importance of this factor is under active investigation using, in part, FT-IR spectrometry and kinetic measurements.

In summary, it has been shown that a reversed-phase HPLC column can be used as a chemical reactor for the chlorination of alkyl phenyl ethers with simultaneous quantitation and separation of reaction products. Furthermore, competition runs have demonstrated that such a column can also impart substrate selectivity to reactions of compounds with the same intrinsic reactivity but different relative hydrophilic/lipophilic characters.

Table I. Individual Monochlorinations at 25°C.

| entry | medium[a] | ether[b] | active chlorine/1[c] | % yld 2 + 3[d] | 2/3[e] |
|---|---|---|---|---|---|
| 1 | column | 1a | 11.0 | 91 | 3.92 ± 0.2 |
| 2 | column | 1e | 1.1 | 50 | 3.43 ± 0.2 |
| 3 | column | 1f | 0.8 | 45 | 4.01 ± 0.2 |
| 4 | column | 1g | 0.8 | 40 | 4.55 ± 0.3 |
| 5 | 95:5 (v/v) $H_2O$-MeCN | 1a | 5.0 | 86 | 1.88 ± 0.1 |
| 6 | 95:5 (v/v) $H_2O$-MeCN | 1e | 5.0 | 87 | 1.24 ± 0.1 |

[a] See text for the procedure of entries 1-4; the reaction time for entries 5 and 6 was 15 min. [b] In entries 1-4, 5 μL of a 0.12 M solution of 1 in MeCN was injected; in entries 5 and 6, [1] = 1.1 x $10^{-4}$ M. [c] Molar ratio of $Cl_2$ plus HOCl (by iodometry) to 1. In entries 1-4, an aliquot of 4.13 x $10^{-2}$ M chlorine water was injected. In entries 5 and 6, a portion of the same solution was added to the reaction mixture to give the indicated ratio. [d] By calibrated HPLC analysis during the run itself for entries 1-4, and of the reaction mixture for entries 5 and 6. For each entry, ±2% for 2-5 runs. [e] Average deviations are given for 2-5 runs.

Table II. Competitive Monochlorinations at 25°C.

| entry | medium[a] | ethers[b,c] | % yld 2 + 3[d,e] |  | 2/3[e,f] |  |
|---|---|---|---|---|---|---|
|  |  |  | LH | HH | LH | HH |
| 7 | column | 1a vs. 1e | 0 | 50 |  | 3.52 ± 0.2 |
| 8 | column | 1b vs. 1e | 0 | 50 |  | 3.28 ± 0.1 |
| 9 | column | 1c vs. 1e | 0 | 50 |  | 3.47 ± 0.2 |
| 10 | column | 1d vs. 1e | 0 | 50 |  | 3.42 ± 0.3 |
| 11 | column | 1e vs. 1f | 0 | 35 |  | 3.98 ± 0.3 |
| 12 | column | 1f vs. 1g | 40 | 35 | 4.03 ± 0.2 | 4.62 ± 0.3 |
| 13 | 95:5 (v/v) $H_2O$-MeCN | 1a vs. 1e | 70 | 76 | 1.71 ± 0.1 | 1.25 ± 0.1 |

[a] See text for procedure of entries 7-12; the reaction time for entry 13 was 15 min. [b] In entries 7-12, 5 μL of a MeCN solution 0.12 M in each ether was injected; in entry 13, [1a] = [1e] = 1.1 x $10^{-4}$ M. [c] Meaningful active chlorine/total 1 ratios are unavailable for entries 7-12; an aliquot of 3.75 x $10^{-2}$ M chlorine water was injected that gave the maximum yield of 2 + 3 from the higher homolog without the formation of disubstituted products. With larger aliquots in entries 7-11, the lower homolog also reacted, but to a lesser extent than the higher homolog. In entry 13, a portion of the same solution was added to the reaction mixture to give active chlorine/total 1 = 2.5. [d] With respect to the total amount of 1, 2, and 3, by calibrated HPLC analysis during the run itself for entries 7-12, and of the reaction mixture for entry 13. For entries 7-12, ±2%, and for entry 13, ±4%, for ≥3 runs. Runs of entry 7 with an internal standard demonstrated that the HPLC yields represent absolute yields. [e] LH = lower homolog; HH = higher homolog. [f] Average deviations are given for ≥3 runs.

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## References and Notes

1. For examples, see (a) Chu, A. H. T.; Langer, S. H. Anal. Chem. 1985, 57, 2197. (b) Tanaka, N.; Hosoya, K.; Iwaguchi, K.; Araki, M. J. Am. Chem. Soc. 1984, 106, 3057. (c) Bolme, M. W.; Langer, S. H. J. Phys. Chem. 1983, 87, 3363. (d) Xie, K. H.; Colgan, S.; Krull, I. S. J. Liq. Chromatogr. 1983, 6(S-2), 125, and references therein.

2. All ethers are known and were prepared by the Williamson procedure (Smith, R. A. J. Am. Chem. Soc. 1933, 55, 3718).

3. This material is a $C_{18}$-bonded stationary phase derived from silica and n-octadecyldimethylchlorosilane; ca. 70% of the silanol groups are derivatized (Scott, R. P. W.; Kucera, P. J. Chromatogr. 1977, 142, 213).

4. Chlorine gas was collected in HPLC-grade water at ca. 5°C to give a stock solution, which contains both $Cl_2$ and HOCl (Zimmerman, G.; Strong, F. C. J. Am. Chem. Soc. 1957, 79, 2063). The total concentration of the two by iodometry (Kolthoff, I. M.; Belcher, R. Volumetric Analysis; Interscience: New York, 1957; Vol. III, p 245) typically was 0.04 M, and the pH 2.1. The solution was stored at 5°C.

5. (a) For the individual reactions, the duration of the gradient begun at t = 20 min was 10 min, and the final MeCN-$H_2O$ compositions and retention times (min) from t = 0 for selected ethers were as follows: 1a: 45% MeCN; 1a, 46.1, 2a, 55.6, 3a, 51.3. 1e: 75% MeCN; 1e, 52.1, 2e, 57.3, 3e, 54.7. 1f: 85% MeCN; 1f, 61.4, 2f, 66.2, 3f, 63.7. 1g: 95% MeCN; 1g, 72.4, 2g, 80.5, 3g, 75.9. (b) As an example, for competition runs between 1d and 1e, the duration of the gradient begun at t = 20 min was 10 min, and the final MeCN-$H_2O$ composition was 60% MeCN. Retention times were as follows: 1d, 62.1, 2d, 72.4, 3d, 68.1; 1e, 73.0, 2e, 90.9, 3e, 81.7. (c) Chlorine water gave a peak at t = 24 min (i.e., 7 min after its injection). In a control the corresponding eluate was collected and by iodometry contained 93% of the active chlorine injected. (d) The void volume of the column was 3.0 mL.

6. A control demonstrated that 1 was within the column when chlorinated.

7. Jaeger, D. A.; Wyatt, J. R.; Robertson, R. E. J. Org. Chem. 1985, 50, 1467; Jaeger, D. A.; Robertson, R. E. Ibid. 1977, 42, 3298.

8. The results of Tables I and II were obtained with several identical columns and did not vary from column to column. Over 130 chlorinations were performed on a single column before its deterioration.

9. Eigen, M.; Kustin, K. J. Am. Chem. Soc. 1962, 84, 1355.

10. The partitioning of $Cl_2$ between $H_2O$ and a hydrocarbon favors the latter (Taylor, N. W.; Hildebrand, J. H. J. Am. Chem. Soc. 1923, 45, 682). HOCl is soluble in polar organic solvents and can yield $Cl_2O$ (Greenwood, N. N.; Earnshaw, A. Chemistry of the Elements; Pergamon: New York, 1984; p 1004).

11. Swain, C. G.; Crist, D. R. J. Am. Chem. Soc. 1972, 94, 3195.

12. For discussions of the detailed nature of bonded phases, see (a) Kelusky, E. C.; Kyfe, C. A. J. Am. Chem. Soc. 1986, 108, 1746. (b) Lochmüller, C. H.; Colborn, A. S.; Hunnicutt, M. L.; Harris, J. M. Ibid. 1984, 106, 4077. (c) Gilpin, R. K.; Gangoda, M. E. Anal. Chem. 1984, 56, 1470, and references therein.

13. It is likely that not all of the MeCN has been removed from the column by the 100% $H_2O$ eluant before injection of the chlorine water aliquot (Gilpin, R. K.; Gangoda, M. E.; Krishen, A. E. J. Chromatogr. Sci. 1982, 20, 345). Controls demonstrated that $Cl_2$ and HOCl do not react with MeCN.

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